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Plasma-Modified Biomaterials for Self-Antimicrobial Applications

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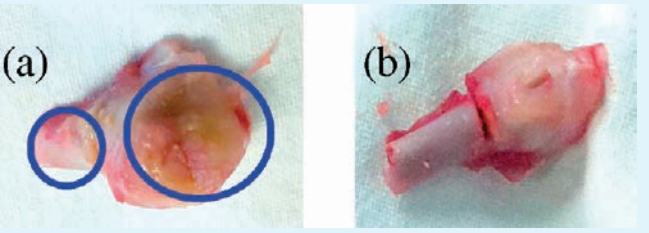
Supporting Information

ABSTRACT: The surface compatibility and antibacterial properties of biomaterials are crucial to tissue engineering and other medical applications, and plasma-assisted technologies have been employed to enhance these characteristics with good success. Herein, we describe and review the recent developments made by our interdisciplinary team on self-antimicrobial biomaterials with emphasis on plasma-based surface modification. Our results indicate that a self-antibacterial surface can be produced on various types of materials including polymers, metals, and ceramics by plasma treatment. Surface characteristics such as roughness, microstructure, chemistry, electronegativity, free energy, hydrophilicity, and interfacial physiochemistry are important factors and can be tailored by using the appropriate plasma-assisted processing parameters. In particular, mechanistic studies reveal that the interfacial physiochemical processes, biocidal agents, and surface free energy are predominantly responsible for the antibacterial effects of plasma-modified biomaterials.



KEYWORDS: plasma surface modification, biomaterials, antimicrobial, self-decontamination

1. INTRODUCTION

Biomaterials such as metals, polymers, ceramics, and composites are widely used in tissue repair and reconstruction. Whether or not the biomaterials and surrounding tissues can coexist and produce synergistic effects depends mainly on the compatibility of the artificial biomaterials such as blood compatibility, osseocompatibility, antibacterial capability, and so on. Surface modification can effectively improve the compatibility by changing the surface chemistry, microstructure, and other materials attributes.[1−3] A critical issue in medical science is bacteria-induced infection during and after surgical operations and it frequently leads to failure of biomaterials and biomedical implants.[4−6] In fact, microbial infection is becoming the predominant cause of biomaterials failure,[7,8] and there are now more than one million infection-related failures annually. The severity stems from that implanted biomaterials are in contact with body tissues and fluids and they sometimes provide a good environment for bacteria to adhere and proliferate, subsequently causing infection of surrounding tissues. Furthermore, there has been excessive use of antibiotics since the introduction of penicillin in the 1940s, especially in developing countries, and some bacteria strains such as the superbug NDM-1 have developed resistance against known antibiotics.[9] Therefore, it is imperative to develop biomaterials with self-antimicrobial ability in order to reduce the chance of postsurgical infection and reliance on externally administered antibiotics during recovery and tissue regeneration.

The current antimicrobial strategies fall into two categories. The first method is to prevent adhesion of microbes on the implant surfaces.[10−12] It has been clinically shown that adhesion of microbe is the earliest and critical step in the pathogenesis of tissue infection. The factors that influence the attachment of bacteria include the structures of the bacteria and surface characteristics of the biomaterials. Several surface modification techniques have been proposed to prevent the attachment and subsequent colonization of microbes, and the most common means is to produce surface structures that reduce or inhibit bacterial adhesion. One of the common methods is to apply zwitterionic or hydrophilic materials like poly(sulfobetaine methacrylate) (pSBMA),[13] poly(carboxybetaine) (pCB)-based materials,[14] and poly(ethylene glycol) (PEG)-based materials,[15] to the surface of biomaterials using atom transfer radical polymerization (ATRP). Because of hydration induced by the electrostatic interaction, the surface nonfouling zwitterionic groups are resistant to nonspecific protein adsorption, bacterial adhesion, and biofilm formation.[14] Hydrophilic materials like PEG-based materials also exhibit good resistance to bacterial adhesion. Recently, Chen and Zheng reviewed the basic antifouling mechanism of polyhydrophilic and polyzwitterionic materials.[15] It is believed that the antifouling ability of these materials is related to the

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surface hydration layer, which serves as a physical and energetic barrier to prevent adhesion of proteins and microbes.[15] Other techniques like covalent or coupling attachment of chemicals, additives, proteins, etc.[16−21] as well as deposition of antiadhesion agents or antibiotics[22] are also used to modify the surface of biomaterials to mitigate bacterial adhesion. For example, Vejborg et al. have shown that an α-tropomyosin coating inhibits attachment of microbes on stainless steel, glass, and polystyrene because of the negative charge.[20] Addition of metals like iron and zinc can prevent biofilm formation by *E. coli* and *P. aeruginosa* by confusing the regulatory system governing the metal ion uptake because some metallic elements are essential to bacterial growth and biofilm formation.[21,23−25] Recent research has also revealed that the proper surface topography and structure can inhibit bacterial adhesion.[26]

In contrast to the first approach, the second common strategy is to kill the bacteria directly using antibacterial agents such as inorganic, organic, and natural germicides. Metals, metal oxides, and compounds composed of biocidal agents are some of the widely used inorganic agents. The antibacterial mechanism of metals is generally believed to be their effects on some proteins and phosphate lipids or penetration through the bacterial membranes resulting in loss of inner materials, cell decomposition, and eventual death of the microbes.[27,28] Furthermore, metal cations can disrupt the division of bacteria resulting in morphological changes and death.[29] The antibacterial effects of organic agents such as quaternary ammonium compounds and aldehyde-based biocides arise from the interference with the cell membrane system or cross-bonding with proteins.[30,31] As a nature biocide, chitosan can prevent the growth of various bacteria.[32] The bactericidal mechanism is believed to be the interaction between the positively charged chitosan molecules and negatively charged microbial cell membranes, resulting in leakage of proteinaceous and associated intracellular constituents as well as alteration of the cell permeability or disruption of the membrane integrity.[33] The related derivatives also exhibit good bactericidal functions.[33,34] In addition, natural and synthesized peptides are important bactericides[35,36] and the death of bacteria arises from membrane permeabilization or nonmembrane-permeabilization of peptides.[37] In membrane permeabilization, the peptide interacts with the phospholipid acyl chains causing considerable membrane fluidization.[37,38] Many peptides have the ability to translocate across the membrane and accumulate in the bacteria cell to either bind to the DNA and RNA or interfere with essential cellular processes such as nucleic acid synthesis and enzymatic activity.[37,39,40]

The success and effectiveness of self-bactericidal biomaterials depend on how these biocides can be incorporated into the biomaterials in a stable and reliable fashion and how to achieve long-term effects such as controlled leaching of the antibacterial agents without compromising the biocompatibility. Because of the non-line-of-sight nature and low processing cost, plasma immersion ion implantation (PIII) is widely used to enhance the biocompatibility of biomaterials and biomedical implants, which typically have complex geometry and surface topography.[41] The technique has also been applied to antibacterial materials.[22,42,43] In this "spotlight on applications", we describe and review recent progress made by our group on surface modification of biocidal biomaterials with emphasis on the relationship between the antibacterial and surface properties of different types of biomaterials.

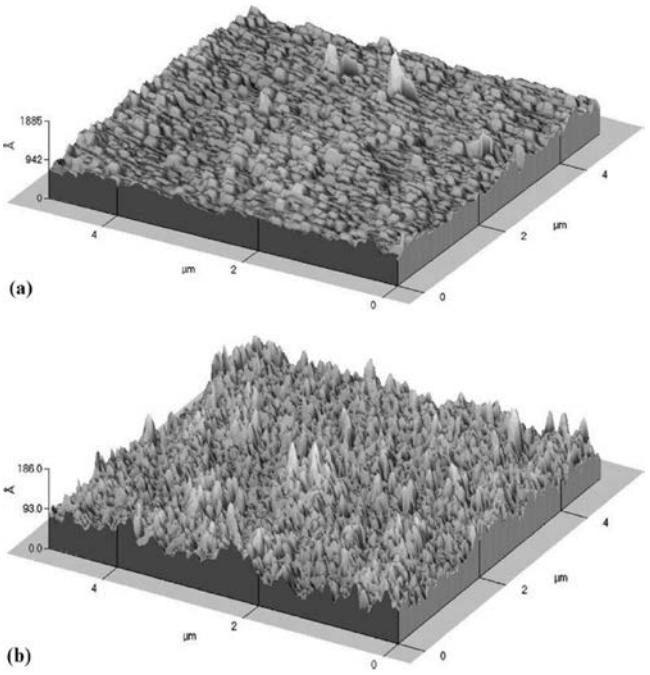

Figure 1. Surface topographies of PET films: (a) the control and (b) C_2H_2 PIII deposited PET films.[44]

2. RESULTS AND DISCUSSION

2.1. Biopolymers. Biopolymers are one of the most important types of functional biomaterials and have been adopted widely in drug delivery systems, tissue regenerative scaffolds for cartilage repair, bone and intervertebral disks, and other biomedical fields. Here, several common and important self-biocidal polymers such as poly(ethylene terephthalate) (PET), polyvinyl chloride (PVC), polyethylene (PE), and poly(butylene succinate) (PBSu) are described.

2.1.1. Plasma-Treated Biopolymers. Surface Characteristics. Surface characteristics such as morphology, roughness, chemical composition, structure, free energy, electronegativity, and hydrophilicity influence the biological and antibacterial behavior of biomaterials. Poly(ethylene terephthalate) (PET) is often machined into artificial blood vessels or artificial heart valve sewing rings in angiocardiopathy.[44] By means of C_2H_2 plasma immersion ion implantation and deposition (PIII&D), an amorphous polymer-like carbon (PLC) film can be deposited on PET. Atomic force microscopy (AFM) discloses that the surface morphology is affected substantially by the plasma treatment. In comparison with the untreated PET, the measured surface roughness (R_a) decreases from 58.9 to 11.2 nm, as shown in Figure 1.[44] In addition, much denser nanoneedles are created on the surface (Figure 1b) and the surface chemical composition is altered as well. After C_2H_2 PIII&D, new radicals of the type R−C≡C−H are created and a mixture of bonds, C═C, C−C, and C═O, together with predominantly C−H, can be detected by Fourier transform infrared spectroscopy (FTIR), Raman spectroscopy, and X-ray photoelectron spectroscopy (XPS).[44] The treated surface becomes more hydrophilic with the contact angle changing from 83.5 to 64.8°. This is consistent with the results reported by Yang that the hydrophobic PET surface can be transformed into a hydrophilic one by argon plasma modification.[45] In practice, a hydrophilic and smooth surface has

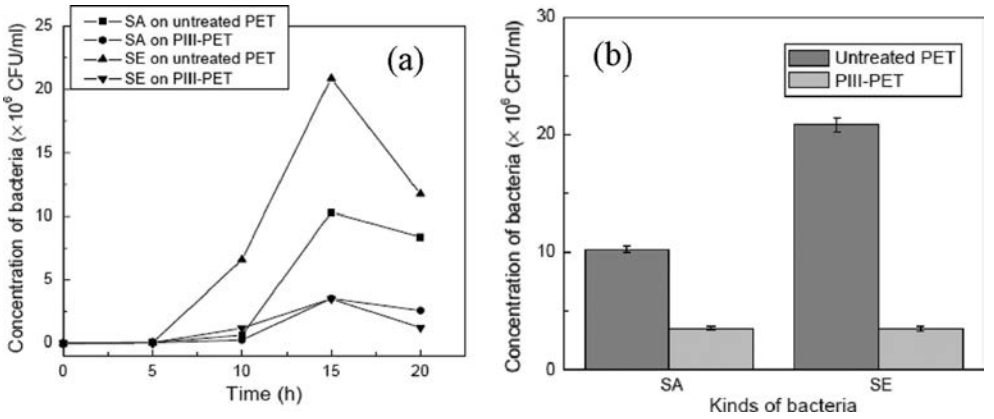

Figure 2. Antibacterial behaviors of PIII-D treated PET. (a) Variation of SA and SE number adhered on the untreated and PIII-D PET; (b) Number of bacteria on the surface of untreated and PIII-D PET after incubation of 15 h. SA, *Staphylococcus aureus*; SE, *Staphylococcus epidermidis*.[44]

less interaction with bacteria, consequently retarding bacteria adhesion.[46]

Antimicrobial Behavior. *Staphylococcus aureus* (*SA*) and *Staphylococcus epidermidis* (*SE*) cultures (37 °C for 24 h) are used to determine the antibacterial performance of pristine and plasma-modified PET. Adhesion of bacteria on both the control and PIII&D PET is a dynamic process as illustrated by Figure 2a. The number of attached bacteria increases with incubation time initially, reaches a maximum value, and then decreases afterward. It is well-known that the early stage after surgery is critical to the prevention of bacterial infection. After bacteria attach and form biofilms on the surface of biomaterials, it is very difficult to remove them. Actually, microbial cells become 10−1000 times more resistant to biocidal agents when they integrate with biofilms.[47] Furthermore, antimicrobial-agent-resistant biofilms can form on different types of artificial implants including artificial hip joints, contact lenses, catheters, cochlear implants, and orthopedic devices.[47−50] Clinically, the ultimate treatment for biofilms is surgical removal of the implants followed by sustained intravenous antibiotics therapy. Therefore, in order to minimize implant failure, the best way is to inhibit bacteria attachment or kill them before the formation of biofilms. In this respect, the PLC samples processed by C_2H_2 PIII&D inhibit early bacteria attachment and colonization as shown in Figure 2b.

2.1.2. Gas Plasma Treatment of Biopolymers. Direct Gas Plasma Treatment. Besides surface treatment by PIII&D, direct implantation of gaseous ions can alter the surface characteristics and antibacterial properties of biopolymers. As one of the common commercial biodegradable polymers, the advantages of poly(butylene succinate) (PBSu) are its excellent processability, biodegradability, harmless degradation products, and noncytotoxicity in the physiological environment.[51,52] However, untreated PBSu does not possess sufficient antibacterial ability, but oxygen and nitrogen PIII can be conducted to enhance the properties. The average water contact angles measured from O−PIII and N−PIII PBSu are 25 and 27°, respectively, which are significantly smaller than the value of about 50° measured from the untreated polymer control.[53] The results are consistent with those observed from other polymers after PIII.[44,45] XPS reveals significant increase in the amount of surface oxygen and nitrogen, respectively and resulting differences in the surface chemistry. As indicated by the high-resolution spectra of C1s, O1s, and N1s in Figure 3, new functional groups like C═NH and $C-NH_2$ are formed on the polymeric surface after N−PIII, whereas C═O is dominant on the oxygen-implanted surface.[53] According to results obtained by plate counting involving two bacteria, *S. aureus* and *E. coli* cultured at 37 °C for 24 h, in comparison with the untreated PBSu, N−PIII significantly suppresses bacterial adhesion on the surface with 91.41% and 90.34% antibacterial effects against *S. aureus* and *E. coli*, respectively, whereas O−PIII only decreases the bacteria number slightly.[53] It implies that the implanted gas species is important to the antibacterial properties. In general, gas plasma ion implantation plays a critical role in repelling bacteria from the polymer when combined with the incorporation of other biocidal reagents. This topic will be discussed further below.

Gas PIII in Conjunction with Biocidal Reagents. The annual demand for poly vinyl chloride (PVC) tubes by hemodialysis is about 370 million meters, and more than 600 000 patients undergo dialysis therapy worldwide.[54] Polyethylene (PE) is also widely used in orthopedic implants.[55] In order to reduce bacterial infection and biofilm formation, biocidal reagents such as triclosan and bronopol can be coated on the surface. However, these reagents are released easily due to poor bonding with the substrate and so the antibacterial effects may not last long enough. As aforementioned, O−PIII can significantly improve the hydrophilicity of biopolymers because more C−O or C═O groups are formed on the surface. After O−PIII, the water contact angles on PVC and PE change from 96 to 20° and 94.7 to 52.6°, respectively.[56,57] To immobilize these biocidal reagents on the polymers, argon PIII is carried out subsequently to form new functional groups such as C═O/C−(Br)C-(NO3)−C on bronopol coated polymers and C═O/C on triclosan-coated polymers.[56,57] In the case of the triclosan-coated PVC, XPS discloses that Ar−PIII creates more C−Cl on the modified surface compared to the unimplanted triclosan coated surface.[56] Formation of new functional groups suggests that the plasma treatment integrates the biocides into the polymer substrate. As shown in Table 1, the plate counting results indicate that the gas-PIII modified polymers generally possess good and durable antibacterial effects. However, the eventual biocidal effects are determined by a combination of factors such as precoated biocide type, plasma gas species, microbial type, polymer type, processing time, and so on. For example, hydrogen plasma implanted PE with precoated bronopol exhibits small biocidal effects against *E. coli*, but better effects are observed from that with precoated triclosan. The Ar−PIII modified PE with precoated bronopol shows reduced antibacterial effects with

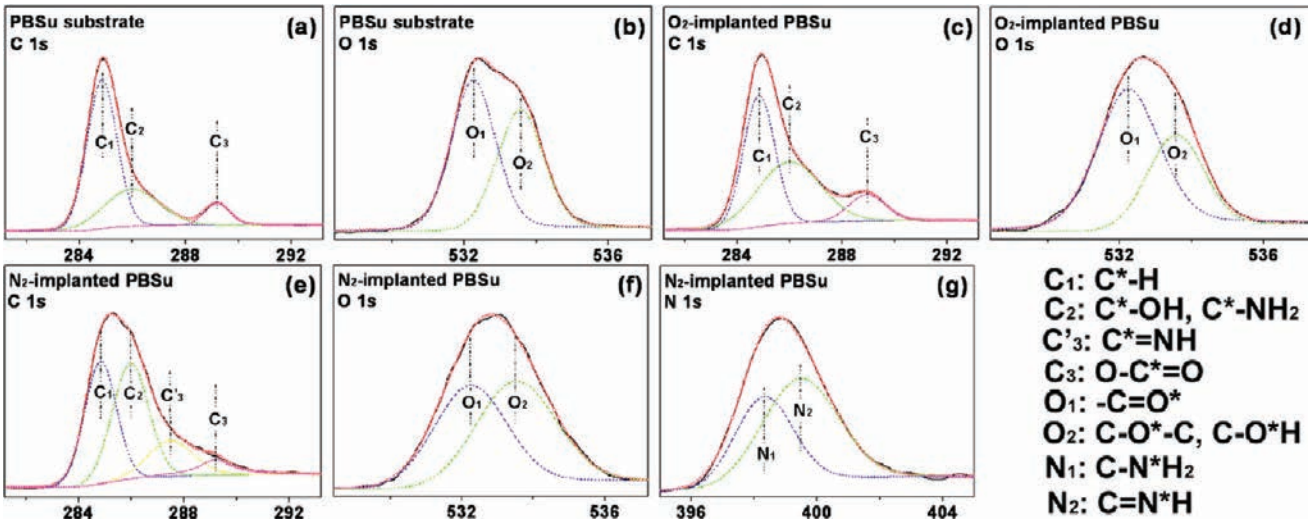

Figure 3. XPS spectra acquired from the surface of PBSu. (a) C1s and (b) O1s from the untreated sample; (c) C1s and (d) O1s from O−PIII PBSu; (e) C1s (f) O1s and (g) N1s from N−PIII PBSu.[53]

Table 1. Antibacterial Effects (%) of Gas-PIII Polymers[56,57]

		S. aureus				*E. coli*			
	plasma modification	0 days	10 days	21 days	42 days	0 days	10 days	21 days	42 days
Ar−PIII	triclosan coated PVC	82.2	73.3			79.6	70.1		
	bronopol coated PVC	98.0	86.7			77.3	69.3		
	triclosan coated PE	99.1		73.8	68.4	99.9		99.9	99.9
	bronopol coated PE	96.2		68.8	62.7	94.7		35.9	13.9
H−PIII	triclosan coated PE	99.8				99.7			
	bronopol coated PE	60.4				20.3			

time, especially against *E. coli*. Although the plasma process can mobilize the biocides on the PVC surface, possible breaking of bonds in the biocide molecule may affect the antibacterial effects. According to the attenuated total-reflection Fourier transform infrared (ATR-FTIR) spectra acquired from the argon plasma-modified sample with precoated triclosan (Figure S1), the peaks at about 1523 and 1333 cm^{-1} can be assigned to the =C−H and C−Cl stretching modes of benzene, respectively, implying that the benzene structure is not fully destroyed during the argon plasma treatment.[56] Therefore, the plasma-treated biocides can retain their antibacterial effects to some extent.

Metals or metal oxides are effective in resisting some bacteria.[27−29] Nevertheless, because of the poor bonding between these bactericides and polymers, degradation of the antibacterial effects when immersed in solutions like simulated body fluids (SBF) is usually too fast.[58−61] Gas PIII in conjunction with metal plasma ion implantation can control and/or decrease the metal release rate in order to optimize the antibacterial effects. Silver and copper are well-known biocidal agents[62−64] in this case. Silver and copper plasma ion implantation can change the surface morphology of PE (Figure 4), and the root-mean-square (rms) roughness values increase after plasma implantation. Although both Ag−PIII and Cu−PIII can significantly enhance the surface hydrophilicity of PE, the latter has a more pronounced effect as shown in Table 2.

Antibacterial tests show that Ag−PIII can give rise to nearly 100% bactericidal effects on PE whereas Cu−PIII yields a slightly smaller value of about 95%.[62] The surface hydrophilicity is one of the factors influencing the surface antibacterial effects, but not the most critical one. XPS depth profiles confirm that both silver and copper are implanted into the PE substrate and have a graded distribution with depth. The evolution of the Cu2p XPS spectra with depth shows that in the top several nanometers, Cu has the bivalence state due to natural oxidation in air, whereas Cu embedded at a greater depth has the zero valence state. Ag−PIII produces similar phenomena and Ag segregates into the substrates as shown in Figure 5. The results show that either Ag or Cu can inhibit or kill bacteria but these metals do not bond with the polymeric matrix or form radicals. This poses the questions on whether these unconfined metal bactericides can easily leach out and if the metal−PIII modified surface has only temporary antibacterial effects. Actually, Ag−PIII or Cu−PIII only endows PE with temporary biocidal ability, as shown in Figure 6, and the antibacterial effects diminish rapidly with immersion time because the metals leach out quickly from the implanted polymer.[60] However, if gas PIII is conducted after metal PIII, release of metals can be suppressed and so more long-term and stable antibacterial effects can be accomplished. However, it does not mean that any gaseous element can fulfill this role. As shown in a and b in Figure 6, N−PIII can complement both Ag−PIII and Cu−PIII PE, but NH_3−PIII does not produce positive

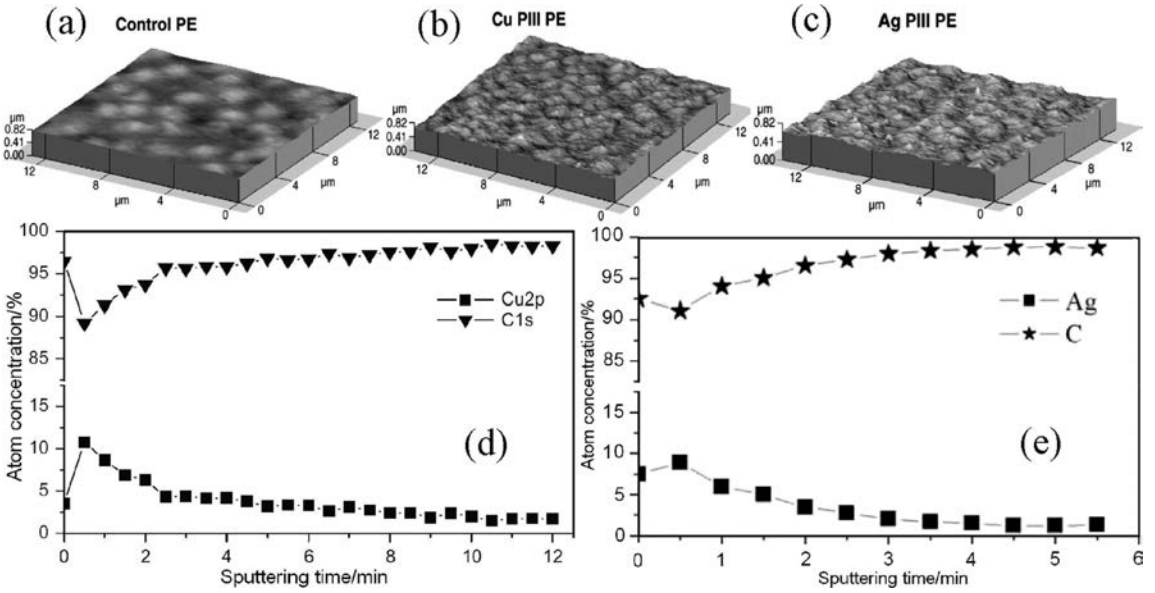

Figure 4. Surface topographies of the untreated and metal plasma implanted PE (a) control PE, (b) Cu−PIII PE, and (c)Ag−PIII PE,[62] as well as the elemental distribution along the depth (d) Cu−PIII PE and (e) Ag−PIII PE.[58,61]

Table 2. Contact Angles of Distilled Water on the Surface of PE[58,61]

	angle (deg)		
	untreated PE	Ag or Ag/N_2-PIII PE	Cu-PIII PE
contact angle	88−87.7	57	47.2

effects following Cu−PIII because C-NH_3 formed by NH_3−PIII does not offer free bonds to prevent the metal from leaching. Although the gaseous element introduced by the second gas PIII process cannot react with the metals in the polymer, it is believed that the newly formed polar functional groups of C═O, C−O, C−N, C═N, and C≡N play an important role in regulating silver or Cu out-diffusion, especially in the case of N−PIII according to chemical analysis.[58−60] Although the aforementioned metal-plasma treated surface like Ag and Cu can produce effective antibacterial ability, it should be mentioned that the released metal ions may lead to some other problems such as environmental issues and toxicity to normal cell or tissues. Therefore, more research must be performed to develop better materials or substitutes.

2.2. Plasma Implanted Titamium. Ti-based alloys are widely used in biomedical fields, especially orthopedic implants, because of their excellent biocompatibility and desirable mechanical properties. Several different processes have been proposed to modify titanium alloys to improve the antibacterial properties[65] and PIII is one of the useful techniques. We have recently implanted silver into titanium by PIII.[66] As shown in Figure 7b, silver is distributed homogeneously on the surface of the Ti sample. The Ag nanoparticles are embedded in the titanium substrate without an abrupt boundary between the implanted layer and substrate, as shown in c and d Figure 7. The selected area electron diffraction (SAED) pattern in Figure 7(c) confirms that the implanted Ag exists as metallic crystals. Coatings produced by thermal spraying and conventional deposition techniques such as chemical vapor deposition

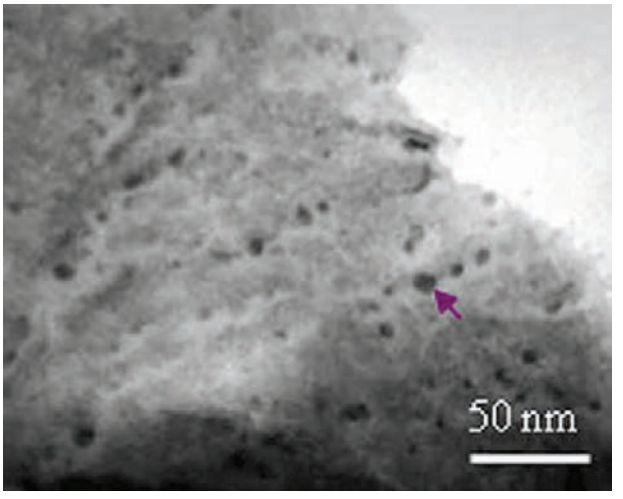

Figure 5. Cross-sectional TEM image of Ag PIII PE.[58]

(CVD) and physical vapor deposition (PVD) have a distinct interface with the substrate. This can result in poor bonding strength between the coating and substrate and possible delamination under stress. Hence, the long-term bactericidal effects can be compromised. The plasma treatment produces a stable silver layer with a near-Gaussian distribution with depth (please refer to the XPS depth profile in ref [66]) and antibacterial tests demonstrates excellent biocidal ability in killing both *S. aureus* and *E. coli*. The size of the embedded silver nanoparticles is affected by the implantation duration and surface zeta potential, and the antibacterial effects can in turn be influenced. The mechanism will be discussed later in this paper.

2.3. Biocidal Films Produced by Plasma-Assisted Technology. Coatings are commonly used to enhance the surface characteristics of biomaterials such as wear resistance,[67] corrosion resistance,[68] ion leaching,[69,70] hemocompatibility,[71] biomimetic property,[72] osteogenesis,[73] as well as general biocompatibility.[74] Some

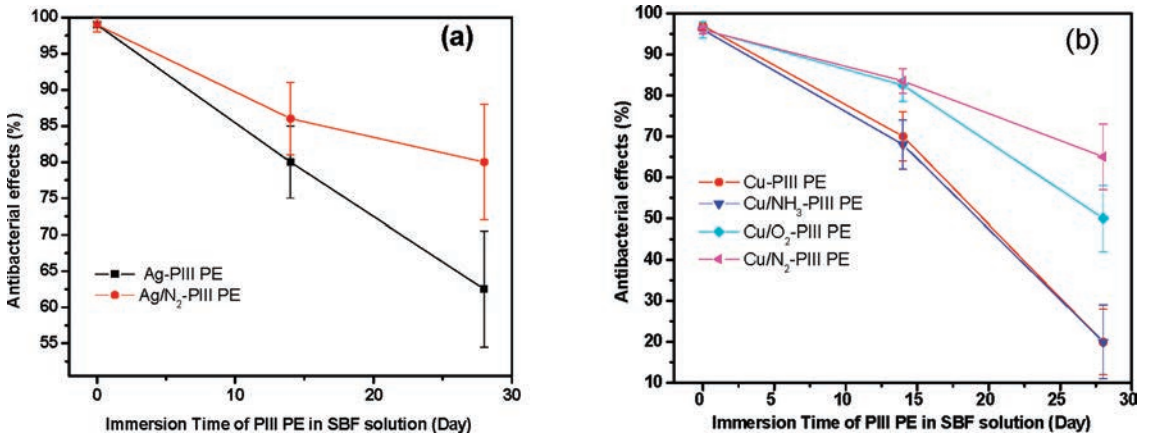

Figure 6. Antibacterial performance of PIII modified PE as determined against *E. coli*. (a) Ag and Ag/N_2 PIII PE at a cell suspension concentration of 1×10^5 CFU/mL,[58] (b) Cu and Cu/gas PIII PE samples with a cell concentration of 1×10^6 CFU/mL.[60]

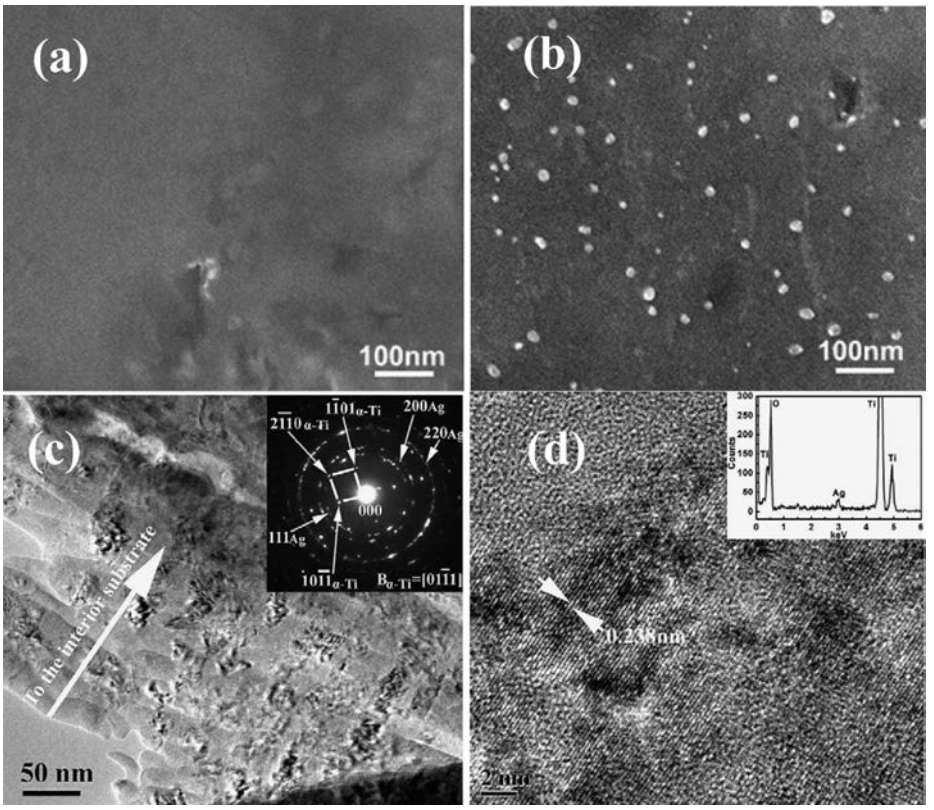

Figure 7. Surface morphology and microstructure after Ti, SEM image of (a) untreated Ti and (b) 1.5 h-Ag-PIII Ti, (c) TEM image acquired from 1.5 h-Ag-PIII, (d) HR-TEM image of 1.5 h-Ag-PIII.[66]

antibacterial films have recently been developed, for instance, self-biocidal films composed of silver, ZnO, and La_2O_3[75,76,71] as well as nonbiocidal films mixed or doped with bactericides.[67,77−80] These two types of biocidal films can be produced by plasma-assisted technology. For example, La_2O_3 films can be produced in a plasma immersion apparatus equipped with a La cathodic arc plasma source.[71] The dual plasma consisting of oxygen and La ions is created by bleeding oxygen gas into the vicinity of the metal arc discharge plume when the cathodic arc is triggered. High-resolution La3d and O1s XPS spectra confirm the formation of a La_2O_3 film which is about 150 nm thick using this dual PIII deposition technique. Plate counting reveals that the antibacterial effects can reach 99.9% against *S. aureus*.[71]

Nonbiocidal films such as titanium nitride and diamond-like carbon (DLC) can be converted into biocidal coatings by Cu or Ag doping.[67,77] A Cu-doped TiN film can be produced by dual magnetron sputtering with layer-by-layer deposition of TiN and subsequent formation of a Cu film. Antibacterial tests show that the effects of this multilayered structure against *E. coli* range from 80% to 90%. According to Tian, et al.,[67] the titanium sputtering time influences the bactericidal effects possibly because it affects the size, shape, and distribution of copper. Similar phenomena

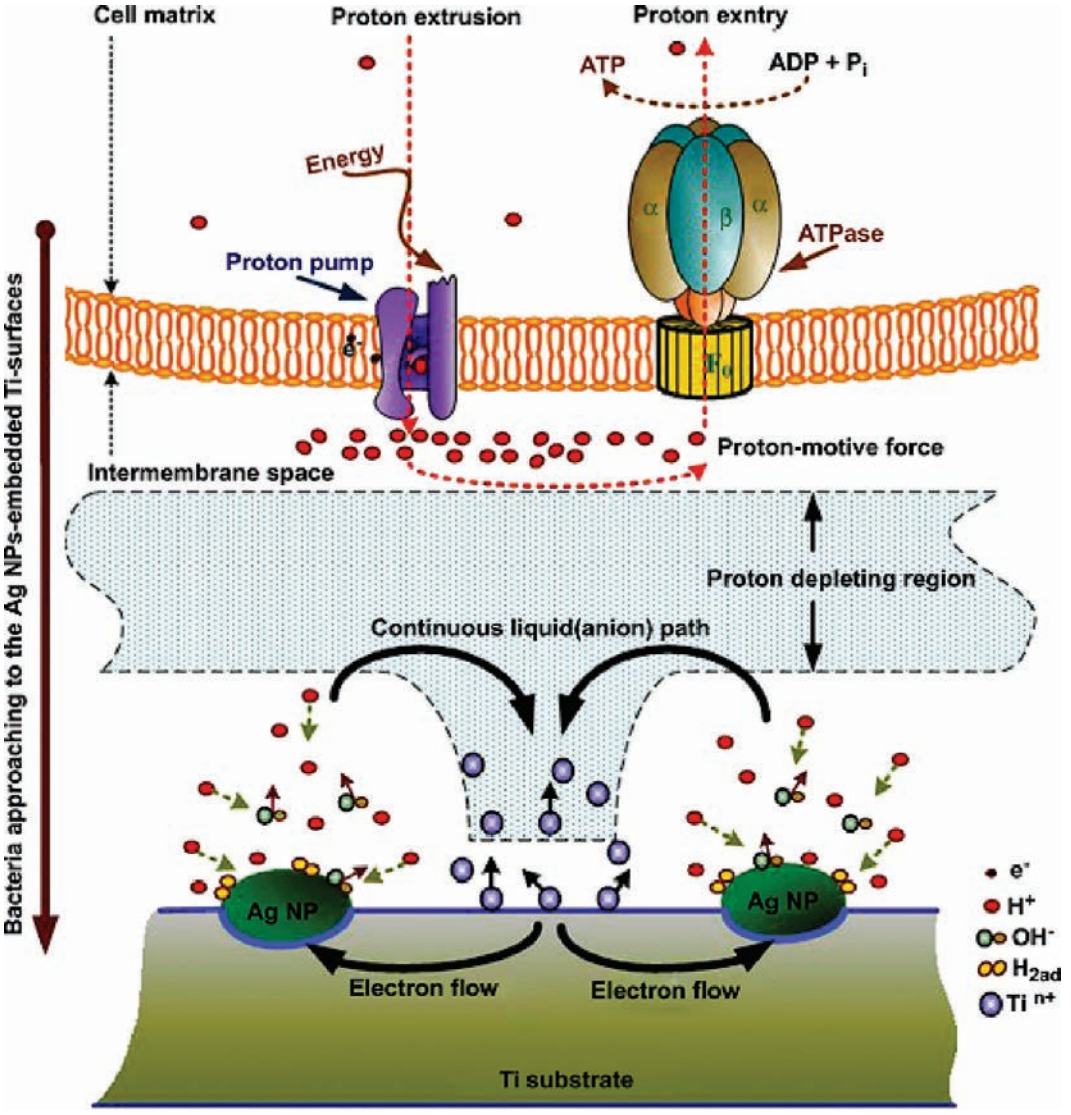

Figure 8. Biocidal mechanism diagram of Ag-PIII treated titanium.[66]

have also been observed for silver.[66,81] Kwok, et al. have fabricated Ag-doped DLC thin films by pulsed filtered cathodic vacuum arc (FCVA) deposition using a coaxial Ag−C target.[77] The surface chemical analysis shows that silver in the Ag-doped DLC film exists in the metallic state.[58,66] The bias voltage has little effects on the antibacterial properties. A high bias voltage applied to the substrate provides C ions with a larger kinetic energy enabling formation of a higher tetrahedral C−C (sp^3) content. On the other hand, Ag doping has no effects on the surface hydrophilicity according to the measured water contact angles, but the process does reduce the interfacial tension of the DLC film in water. The Ag-doped DLC films show high bactericidal effects of over 98% against *E. coli*.[77]

2.4. Biocidal Mechanism. The biocidal mechanism of antibacterial agents is quite complex. Plasma surface modification changes the chemical composition, hydrophilicity, topography, roughness, zeta potential, as well as interfacial energy. Generally, plasma modification often improves the surface hydrophilicity of biopolymers.[44,53,56−59] Our results reveal that hydrophilicity favors adhesion of organic biocidal agents onto the surface but does not determine the biocidal effects directly. The newly formed functional groups like R-C≡C−H, C═NH, and C-NH_2 change both the interfacial potential and surface free energy. Most bacteria cell walls are negatively charged because of teichoic, lipoteichoic, and teichuronic acids in the cell membranes.[82,83] The Coulombic force from the negatively charged surface functional groups can repel bacteria and enhance the antibacterial effects. However, both the untreated PET and cp-titanium with a more negative zeta potential exhibit the worst antibacterial effects compared to the plasma modified biomaterials.[44,66] Hence, it is believed that the adhesion process is not dictated solely by electrostatic interactions between the bacteria and substrate. The interfacial free energy of adhesion (ΔF_{adh}) between the bacteria and substrate is believed to play a crucial role in the inhibition of bacteria attachment.[84] That is, if $\Delta F_{adh} > 0$, the bacteria adhesion process cannot be supported. In Wang's experiments,[44] the PLC film fabricated by C_2H_2 PIII shows higher ΔF_{adh} values of 3.1 and 15.5 mJ/m^2 against *Staphylococcus aureus* and *Staphylococcus epidermidis*, respectively, whereas the corresponding values determined from the untreated PET are −20.9 and −28.5 mJ/m^2, respectively. This is in good agreement with the aforementioned antibacterial results.[44]

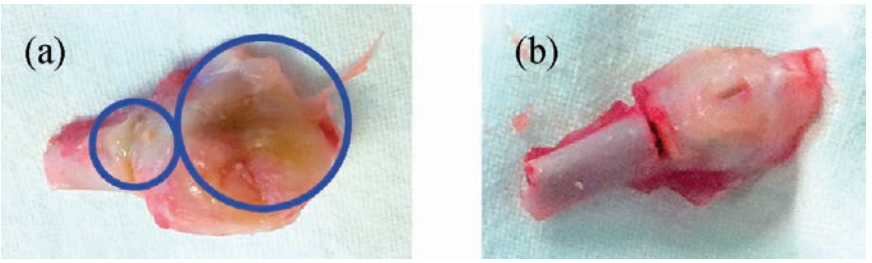

Figure 9. Bacterial infection conditions of bone tissues surrounding Ti6Al4 V implants with preinjection of *S. aureus* 10 000 CFU/10 μL. (a) The untreated sample with pus indicated by blue circles, and (b) PIII-treated sample without pus.[85]

Metal embedded films or metal oxide films produced by plasma-assisted technology kill bacteria directly or via some reactions.[58−62,67,77] It is believed that copper or silver released from the treated biomaterials adhere to the bacteria cell surface, penetrate the cell membrane, bind to the functional groups of proteins, induce protein denaturation, degrade the cytoplasm, and finally causing cell death.[63,64] However, the biocidal mechanism should be reconsidered when the substrates are also metallic materials and have corrosion potentials that are different from those of the embedded metallic particles. Cao and Liu's recent research reveals that killing results from the transfer of protons from the inside to the outside of the bacteria driven by microgalvanic reactions.[66] The schematic diagram of this mechanism is illustrated in Figure 8. Because Ti and embedded Ag have different potentials, each Ag particle and Ti substrate will constitute one microgalvanic couple when immersed in an electrolyte solution with the embedded Ag particle serving as the cathode and Ti being the anode. The subsequent cathodic reactions occur in the proton depleted regions between the bacteria cell membrane and titanium. This disrupts the proton electrochemical gradient in the intermembrane space of the bacteria and interferes with adhesion and proliferation. The disruption of the transmembrane proton electrochemical gradient may inactivate the adenosine triphosphate (ATP) synthesis, ion transport, and metabolite sequestration, finally inducing death of the bacteria.[66]

A common orthopedic biometal, Ti6Al4 V alloy, has been subjected to gas-PIII. The bacteria cultures suggest that oxygen PIII pretreatment with ensuing H_2O PIII yields an antibacterial effect of 42.42% against *S. aureus* (ATCC 29213) in vitro. This is the common pathogen found in orthopedic infection. The amount of attached bacteria on the surface of the PIII modified alloy is lower than that on the untreated control. In order to further evaluate the antibacterial performance in vivo, 10 000 CFU/10 μL *S. aureus* are injected into the femoral canal of a mouse. Afterward, a titanium rod 2 mm in diameter and 20 mm long is implanted into the canal by the retrograde approach. A total of twelve mice are implanted with the untreated and treated titanium nails and four of them are sacrificed after operation. Pus, abscess formation, cortical lysis, and joint effusion are observed from the biopsies implanted with untreated Ti rods, whereas such infection signs are not observed from the bones implanted with the surface treated Ti rods as shown in Figure 9.[85] The observation show that H_2O PIII can suppress bacterial infection under in vivo conditions, and it is in line with many in vitro studies. Gas PIII generally increases the surface roughness of Ti-based alloys, and some nanoscale needlelike or islandlike structures are observed on the surface.[86,87] In addition, gas PIII can induce dealloying in the near surface leaving independent Ti, Al, or V atoms scattered in these needlelike or islandlike structures. Because Ti, Al, and V have different standard electrode potentials of −1.630, −1.662, and −1.13 V, respectively, the protons produced by the microgalvanic couple reactions in the electrolyte solution will inactivate the bacteria as observed by Cao and Liu.[66]

3. CONCLUSION

In summary, plasma-based technology is suitable for the development of self-antibacterial biomaterials such as polymers, metals, and ceramics. The chemical compositions and microstructures can be tailored in order to produce the desirable functions and biocidal properties. The antibacterial effects of biopolymers can be enhanced by introducing new functional groups or bactericidal metals into the surface. Immobilization of organic biocidal reagents on the surface is also a good strategy. Some specific plasma-assisted modification techniques like dual PIII processes or magnetron sputtering can produce biocidal films directly with bactericidal agents. The antibacterial properties of biometals such as titanium and titanium alloys can be improved by metal-PIII or gas-PIII. In vitro and in vivo results reveal that the plasma induced antibacterial mechanism is quite complex. It is affected by the surface roughness, surface chemistry, electronegativity, surface free energy, microstructures, hydrophilicity, and interfacial physiochemistry. Among these various factors, it is believed that the biocidal chemicals, surface free energy, and interfacial physiochemical processes are most critical from the perspective of antibacterial effects. Some biocidal agents such as Ag, Cu, La_2O_3, and organic bacterial reagents can react with the cell membrane or other internal contents to induce death of the bacteria. Interfacial physiochemical processes like microgalvanic couple reactions may be another factor for bacteria killing because the protons can disturb the normal biological course of bacteria. The higher interfacial free energy between the bacteria and substrate as a result of plasma treatment enhances the antibacterial effects.

4. EXPERIMENTAL SECTION

In this mini-review, we describe the results obtained from C_2H_2 plasma immersion ion implantation and deposition (PIII&D) of PVC, gas plasma immersion ion implantation of biopolymers, metal plasma immersion ion implantation of polymers, gas and metal dual plasma immersion ion implantation, Ag-doped DLC films, dual plasma immersion ion implantation and deposition, gas plasma immersion ion implantation of titanium alloys, metal plasma immersion ion implantation of titanium, and plasma-assisted dual magnetron sputtering. For the detailed experimental procedures and biological tests, readers are referred to the following references: 44, 60, 61, 58, 77, 71, 86, 66 and 67. More details about plasma-assisted technologies are available from ref 41.

■ ASSOCIATED CONTENT

Supporting Information. ATR-FTIR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Plasma-Modified Biomaterials for Self-Antimicrobial Applications

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Supporting information

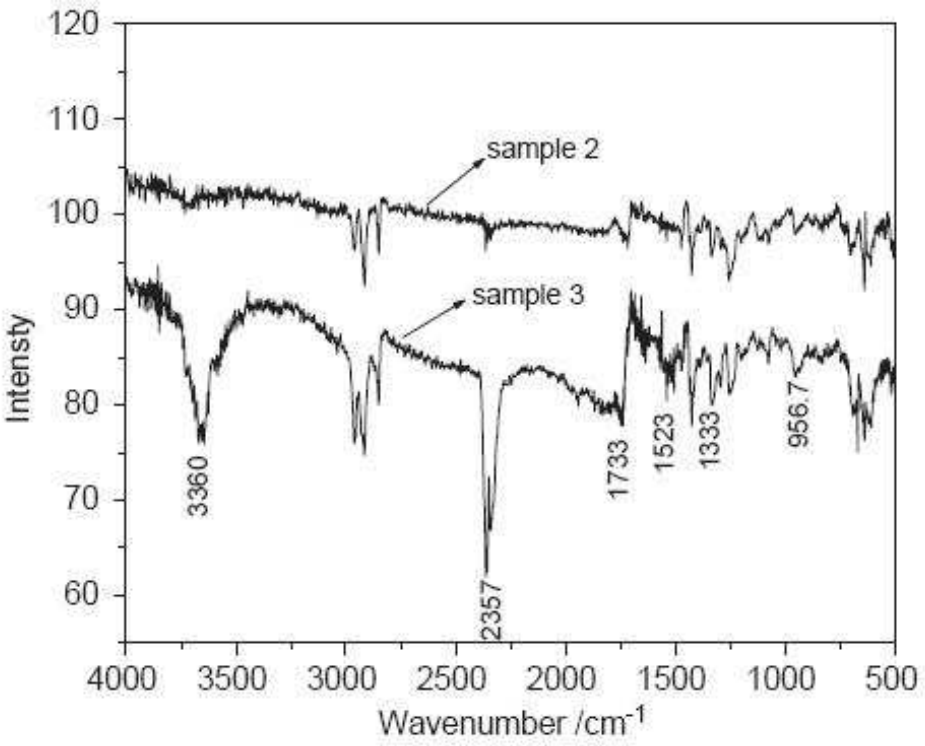

Figure S1: ATR-FTIR spectra acquired from PVC samples. Sample 2 was treated by oxygen plasma only. And sample 3 was modified with an oxygen plasma, coated with triclosan, and then treated with an argon plasma (56)