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Formation of contact active antimicrobial surfaces by covalent grafting of quaternary ammonium compounds

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ABSTRACT

Different synthetic strategies for the formation of contact active antimicrobial materials utilizing covalent linkage of quaternary ammonium compounds (QACs) were reviewed. There is a demand to find methods that will prevent bacterial fouling without the release of antimicrobial agents, because biocides cause environment pollution and promote the development of bacteria resistance mechanisms. The contact active antimicrobial surfaces may provide a useful tool for this purpose. The covalent surface grafting of QACs seems to be a feasible and promising approach for the formation of safe and effective antimicrobial materials that could be utilized for medical devices, food industry, water treatment systems and other applications. This manuscript reviews covalent attachment of QACs to form contact active antimicrobial materials based on glass, metals, synthetic and natural polymers. The review emphasizes the description of different synthetic methods that are used for the covalent linkage. Direct covalent linkage of QACs to the material surfaces, a linkage via auxiliary nanoparticles (NPs), or spacers, controlled radical polymerization techniques and a linkage to pre-activated surfaces are discussed. The physico-chemical properties and biological activity of the modified surfaces are also described. This review does not cover non-covalent grafting of QACs and incorporation of QACs into a bulk material.

1. Introduction

Control of microbial growth on material surfaces is a subject of high scientific and practical significance. Harmful microorganisms growing on surfaces of medical devices, food processing and water treatment systems, filters etc. leads to diseases, contamination, spoilage and other damages [1–3]. Microorganisms can also build biofilms on materials surfaces. Microbial cells embedded in biofilm are up to 1000 times more resistant in comparison with planktonic cells. Therefore, the biofilms present a persistent source of microbial contamination that can be hardly eliminated [4–6]. Numerous antimicrobial agents are currently used to prevent the undesired microorganisms' growth. However, extensive usage of these agents may cause environmental pollution, public health damages and promote development of bacteria resistance mechanisms resulting in the formation of multidrug resistant species [7,8]. Thus, there is a current demand to find new treatments that will enable the control of microbial growth without massive release of antimicrobial agents to the environment [9,10]. In the recent decade, new strategies that aim to decrease the amount of used antimicrobial agents have been developed.

The first approach is superhydrophobic surfaces (contact angle value > 150°) that diminish bacterial adhesion, rather than killing them directly, and enable to reduce biofilm formation without the use of biocides [11–13]. The second approach is the contact active antimicrobial materials. In contact active materials an antimicrobial moiety is attached to a material surface and kills the bacteria without being released [14–18]. Unlike superhydrophobic surfaces that provide an elegant solution for bacterial adhesion prevention, contact active materials can be used in applications where the physical elimination of microorganisms is also necessary [19,20]. Since the antimicrobial agent is not released, the contact active materials do not contribute to the environmental pollution and also retain their effect after multiple usages. Therefore, this approach allows minimizing the amount of the active agent needed to prevent microbial growth [21,22]. Due to these environmental and operational advantages, contact active antimicrobial materials are of high applicative interest [23–27]. Numerous approaches for grafting of antimicrobial moieties on material surfaces, such as covalent linkage, sonication [28–30], hydrogen bonding [31,32], hydrophobic interactions, electrostatic interaction [33] and metal-coordination chemistry [34,35] were reported. Covalent linkage represents one of the most effective approaches for a formation of stable and reliable contact active antimicrobial materials [36,37]. The strong covalent linkage ensures that the bioactive compound will not migrate to the environment, which is extremely important for biomedical, water

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Table 1
Contact active antimicrobial surfaces prepared by covalent grafting of quaternary ammonium compounds (chemical formula, antimicrobial activity, surface kind and reference to the relevant research).

Ref	QAC name/chemical formula or QAC precursor	Antimicrobial activity	Kind of surface
[22]	tetraethoxysilane (TEOS) and $Q_4N^+ - Si(OR)_3$	*S. Aureus* and *E. Coli*	glass substrates
[25]	N-(4-Benzoylbenzyl)-N,N-dimethylbutan-1-aminium Bromide: $C_{28}H_{36}NO$	*S. Aureus* and *E. Coli*	plastics, textiles and alkylated glasses
[50]	3-(trimethoxysilyl) propyldimethyloctadecyl ammonium chloride: $C_{26}H_{58}ClNO_3Si$	*S. Aureus* and *E. Coli*	cotton cloth and glass
[51]	octadecyldimethyl (3-trimethoxysilylpropyl) ammonium chloride: $C_{26}H_{58}CiNO_3SI$	*S. Aureus, E. Coli* and *P. Aeruginosa*	microfibrillated cellulose
[52]	dimethyloctadecyl [3-(trimethoxysilyl) propyl] ammonium chloride: $C_{26}H_{58}CiNO_3SI$	*E. Coli, MS2 Coliphage, Poliovirus type 3* and *Adenovirus type 2*	silica sand
[53]	trimethoxysilylpropyl octadecyldimethyl ammonium chloride: $C_{26}H_{58}NO3SiCl$	*B. Cereus, A. Acidoterrestris, E. Coli* and *P. Aeruginosa*	glass, polyvinyl alcohol and cellulose
[54]	poly(2-(dimethylamino) ethyl methacrylate) (PDMAEMA$(C_9H_{18}ClNO_2)_n$ was a precursor of poly quaternary ammonium which grown from the surface of polypropylene	*E. Coli*	polypropylene
[55]	trimethoxysilylpropyl trimethyl ammonium chloride (QAC-C0): $C_9H_{24}ClNO_3Si$ or trimethoxysilylpropyl octadecyldimethyl ammonium chloride (QAC-C18): $C_{26}H_{58}NO_3SiCl$	*E. Coli* and *S. Aureus*	regenerated cellulose membrane surfaces
[57]	3-(trimethoxysilyl)-propyldimethyloctadecyl ammonium chloride: $C_{26}H_{58}NO_3SiCl$	*S. Aureus, S. Epidermidis, E. Coli* and *P. Aeruginosa*	silicone rubber
[58]	3-(trimethoxysilyl)-propyldimethyl-octadecyl ammonium chloride: $C_{26}H_{58}NO_3SiCl$	*C. Albicans* and *S. Mutans*	titanium
[59]	dimethyloctadecyl [3-(trimethoxysilyl) propyl] ammonium chloride: $C_{26}H_{58}ClNO_3SiCl$, trimethyl [3-(trimethoxysilyl) propyl] ammonium chloride: $C_9H_{24}ClNO_3Si$	*E. Coli, S. Enterica* and *B. Subtilis*	polyethylene and polystyrene −based films
[60]	3-(trimethoxysilyl) propyl dimethyloctadecyl ammonium chloride: $C_{26}H_{58}NO_3SiCl$	*E. Coli, B. cereus* and *multidrug resistant to P. Aeruginosa*	metal, stainless steel
[61]	trimethoxysilylpropyl octadecyldimethyl ammonium chloride: $C_{26}H_{58}NO_3SiCl$	*E. Coli* and *S. Aureus*	alginate nanoparticles grafted on cellulose textile fibers
[62]	trimethoxysilyl)-propyldimethyloctadecyl ammonium chloride: $C_{26}H_{58}NO_3SiCl$	*E. Coli, S. Aureus* and *D. Geothermalis*	silica nanoparticles grafted on glass surface
[63]	2,3-epoxypropyl trimethylammonium chloride: $C_6H_{14}NOCl$	*B. Subtilis, S. Aureus* and *E. Coli*	microfibril cellulose
[64]	2,3-epoxypropyl trimethylammonium chloride: $C_6H_{14}NOCl$		nanofibril cellulose for high water absorbency
[65]	poly-2-dimethylaminoethyl methacrylate: $C_{10}H_{20}NO_2$	*E. Coli*	glass substrates
[66]	binary polymer composed of partially quaternized linear copolymer poly (DMAEMA-co-MMA) and ethylene glycol dimethacrylate (EGDMA)	*E. Coli* and *S. Epidermidis*	glass slides
[67]	reaction between hexamethyldisiloxane (on the surface) and ethylenediamine. Then, thylenediamine react with hexyl bromide and further methylation by methyl iodide to form tertiary ammonium groups on the surface	*S. Aureus* and *K. Pneumoniae*	stainless steel and cellulose-based filter paper
[70–72]	quaternary ammonium polyethyleneimine	*S. Aureus, E. Coli* and *S. Mutans*	polyethyleneimine nanoparticles
[73]	quaternary ammonium polyethylenimine nanoparticles	*S. Aureus, P. Aerogenous, E. Coli* and *H. Plate*	polyethylene vinyl acetate or polyethylene methacrylic acid surfaces
[74]	tertiary amino groups of polyurethane were converted into quaternary ammonium	*E. Coli* and *S. Aureus*	polyurethane membrane
[78]	2-(dimethylamino)ethyl methacrylate (DMAEMA): $CH_2 = C(CH_3)COOCH_2CH_2N(CH_3)_2$.	*E. Coli* and *B. Subtilis*	filter paper
[79]	2-(Dimethylamino)ethyl methacrylate (DMAEMA): $CH_2 = C(CH_3)COOCH_2CH_2N(CH_3)_2$.	*E. Coli*	cellulose fiber
[80]	iodine containing quaternary amine methacrylate copolymers	*E. Coli* and *S. Aureus*	iodine containing quaternary amine methacrylate copolymers
[82]	3-(trimethoxysilyl)-propyldimethylocta decylammonium chloride: $C_{26}H_{58}ClNO_3Si$	*E. Coli*	polyurethene catheters
[83]	The poly(ethylene terephthalate) film was first graft copolymerized with 4-vinylpyridine and subsequently derivatized with hexyl bromide via the quaternization of the grafted pyridine groups into pyridinium groups	*E. Coli*	cellulosic materials

treatment and food applications [38,39].

Quaternary ammonium compounds (QACs) have potent antimicrobial activity and were found to be effective against various bacteria, including multidrug resistant strains [40–43]. Although the working mechanism of the QACs is not fully understood, its antimicrobial effect is related to strong affinity and damaging interactions between the positively charged quaternary nitrogen of the QACs and the negatively charged head groups of acidic phospholipids in microorganisms membranes [44,45]. In addition, it was reported that the polarity and steric properties have significant effect on the antimicrobial potential of QACs [40]. Due to their high variability, low cost and outstanding antimicrobial activity, QACs have drawn much interest. Surface attachment of QACs towards formation of contact active antimicrobial materials is highly desired, since it can minimize toxicity and environmental damage of these compounds and diminish bacterial resistance promotion [42,46–48]. Jiao et al. recently published a review that describes potential toxicological and antimicrobial resistance of QAC's including biomedical applications containing biomaterials that are based on randomized human clinical trials, the golden standard in contemporary medicinal science [43].

This manuscript reviews covalent attachment of QACs to form contact active antimicrobial surfaces based on various materials such as glass, metals, synthetic and natural polymers (Table 1). The review emphasizes description of synthetic methods that are used for the covalent linkage. Direct covalent linkage of QACs to the material surfaces, a linkage via auxiliary nanoparticles (NPs) or spacers, controlled radical polymerization techniques and a linkage to pre-activated surfaces are discussed. This review does not cover non-covalent grafting of QACs and incorporation of QACs into a bulk material.

2. Synthetic methods for covalent linkage of quaternary ammonium compounds (QACs)

There are two main synthetic approaches, "linking tail-active head" and "*in situ* quaternization of tertial amines", that are utilized for covalent bonding of QACs on the materials surfaces.