Quaternary ammonium compounds in dental restorative materials

Yu ZHANG1*, Yinyin CHEN2,3*, Yuntong HU2, Fang HUANG2 and Yuhong XIAO2,4

1 The Affiliated Stomatological Hospital of Kunming Medical University, Kunming, Yunnan, China
2 Department of Stomatology, Kunming General Hospital of Chengdu Military Command, Teaching Hospital of Kunming Medical University, Kunming, Yunnan, China
3 Kunming Municipal Stomatological Hospital, Kunming, Yunnan, China
4 Center for Dental Research, School of Dentistry, Loma Linda University, Loma Linda, California, USA

Corresponding author, Yuhong XIAO; E-mail: xiaoyuhong56@126.com

Quaternary ammonium compounds (QACs) have been used widely in medicine, owing to their antimicrobial properties. They also have strong permeability, stable performance, low skin irritation, low toxicity, low corrosion, lasting biological effects and so on, comparing with other antimicrobial agents. At the end of last century, polymerizable quaternary ammonium antimicrobial monomers had been synthesized and applied in dentistry, in order to reduce or prevent microbial biofilm formation on dental materials surfaces. This review aims to discuss the current progress of QACs applied in composite resin, adhesive systems, acrylic resin, glass ionomer cement and endodontic materials, regarding to their antimicrobial potential, mechanical properties, and biocompatibility.

Keywords: Quaternary ammonium compounds, Dental materials, Composite resins, Dentin bonding agents, Root canal filling materials

INTRODUCTION

Quaternary ammonium compounds (QACs) are derivatives of ammonium compounds, in which all four of the hydrogen bonded to nitrogen have been replaced with hydrocarbyl groups. The general formulas is RNX, four R, hydrocarbyl, which can be the same or different, additionally X is halogen anion in most case and can be also acid radical, such as HSO4, RCOO, etc. The schema of polymerizable and unpolymerizable QACs were shown in Fig. 1. QACs have excellent antimicrobial properties, also, they also have strong permeability, stable performance, low skin irritation, low toxicity, low corrosion, lasting biological effects and so on, comparing with other antimicrobial agents. Therefore, they have been widely used in industry and pharmaceutical industry1,29.

In 1994, Imazato had synthesized, for the first time, a quaternary ammonium dental antimicrobial monomer —12-methacryloyloxydodecylpyridinium bromide (MDPB) with potent antimicrobial properties by combinating quaternary ammonium groups with methyl acryloyl groups. The structure was similar to cetlypyridinium chloride (CPC), which was applied in mouthwash and toothpaste as antiseptic additive30. Thereafter, studies reported31 that methacryloyl groups and aliphatic quaternary ammonium groups were combined, then quaternary ammonium antimicrobial monomer containing different alkyl chain lengths was developed. Besides that, the antimicrobial properties of these monomers was evaluated by the authors, and methacryloyethyl cetyl ammonium chloride (DMAE-CB) with the best antimicrobial activity was screened out, thus suggesting that the antimicrobial properties of QACs were related to the alkyl chain length of quaternary ammonium groups32. In addition, several studies demonstrated that MDPB and DMAE-CB were lethal to both planktonic and biofilm forms of varied cariogenic bacteria, and they could kill more than 90% of the bacteria within 60 s at high concentrations33,34.

In recent years, scholars have done a great deal of exploration from the following two aspects in order to improve the performance of quaternary ammonium antimicrobial monomer. Some scholars aimed to develop antimicrobial monomer with double quaternary ammonium groups. For instance, Caillier et al.5,6 had attained a novel antimicrobial monomer by combining two quaternary ammonium groups with one polymerizable group, whose antimicrobial activity was better than quaternary ammonium antimicrobial monomer with a single chain. Besides, Huang et al.10 developed two novel crosslinking antimicrobial monomers. These monomers had two aliphatic C=C in their molecular structures, and it was likely that more antimicrobial monomers could be incorporated into resin matrix when polymerized with resin matrix, and antimicrobial activities of materials incorporating these monomers would be greatly improved. Antonucci11 and Cheng et al.12 have successfully synthesized two crosslinking antimicrobial monomers with two polymerizable groups by Menschutkin reaction13, and their polymerization performance were also greatly improved.

With the development of quaternary ammonium antimicrobial monomer, more and more antimicrobial materials are emerging constantly. However, it brings a series of adverse effects to the materials, such as color or mechanical properties change etc. In this review, we discuss that QACs was incorporated into dental materials, such as composite resin, adhesive systems, acrylic resin, glass ionomer cement and root canal...
fillings, highlighting aspects regarding microorganism growth inhibition, cytotoxicity, and physical properties of these modified materials.

COMPOSITE RESIN

Dental caries is the most common and widespread oral disease, having as the main etiologic agent the acidic attack from cariogenic bacteria, such as Streptococcus mutans (S. mutans), Lactobacillus spp., and actinomyces etc.[14,15]. Currently, the most widely dental material used to treat caries lesions is composite resin, especially because of its excellent esthetics, load-bearing and plastic properties[16-18]. However, composite restorations do not have antimicrobial property and they could accumulate more biofilm than other restorative materials[19-21]. It has been shown that there is microleakage on restoration margins, and these gaps can be colonized by oral bacteria, thus resulting in secondary caries, which makes the restoration replacement necessary[22,23].

In order to prevent or diminish biofilm accumulation over composite and in the restorations margins, and also to improve the durability of prostheses, antimicrobial restorative materials have been developed, especially through the incorporation of quaternary ammonium to composite resins[24-32]. In 2006, a research developed by Beyth et al.[24] reported that 1 wt% quaternary ammonium polyethyleneimine (QPEI) nanoparticles immobilized into composite or fluid resin had strong antimicrobial activity upon contact without leach-out of the nanoparticles and compromising in mechanical properties. Cheng et al.[25-27] performed studies incorporating of nanoparticles of amorphous calcium phosphate (NACP), quaternary ammonium dimethacrylate (QADM), and nanoparticles of silver (NAg) into composite resins. The results had shown that modified resins greatly decreased biofilm metabolic activity, colony-forming unit (CFU), and lactic acid with strong and durable antimicrobial properties and remineralization, while matching the load-bearing capability of commercial composites without antimicrobial properties. In similar studies, Huang et al.[28,29] developed resins containing 10 wt% of polymerizable QACs, 2-methacryloxylethyl dodecyl methyl ammonium bromide (MAE-DB) or 2-methacryloxylethyl hexadecyl methyl ammonium bromide (MAE-HB). And they compared these new compounds with unmodified resins. It has been observed that modified resins disturbed the integrity of S. mutans and depressed expression of the bacterial glucosyl transferases (gtf B and gtf C). Therefore, modified resins had strong and long-lasting antimicrobial effects. Besides that, 2-Dimethyl-2-dodecyl-1-methacryloxyethyl ammonium iodine (DDMAI) was added into a resin system by He et al., and they found that DDMAI could endow resin system with radiopacity and antimicrobial effectiveness without compromising in mechanical properties[30]. Then, a series of antimicrobial quaternary ammonium methacrylate monomers (QAM) with different substituted alkyl chain lengths (from CL10 to CL18) were incorporated into commonly used dental resin as immobilized antimicrobial agents by above authors. It has been demonstrated that dental resin containing CL16 and CL18 had the best inhibitory effectiveness on both young biofilm and mature biofilm without compromise in double bond conversion (DC), flexural strength (FS), and flexural modulus (FM) between dental resin with and without QAM[31]. Similarly, Liang et al.[32] added four novel QADM monomers named IMQ (side alkyl chain length from 12 to 18) into dental resin. According to the mechanical properties and the biofilm inhibitory effect, dental resin containing IMQ with CL16 had the best comprehensive properties, while the optimal concentration of IMQ with CL16 in dental resin would be in the range of 5–10 wt%. And then, 2-methacryloyloxyethyl phosphorylcholine (MPC) was incorporated into a dental composite in a study performed by Zhang et al.[33]. Their results suggested that incorporation of MPC into composites at 3% greatly reduced protein adsorption, bacteria attachment, and biofilm CFUs without compromising mechanical properties. We can contribute this to that MPC has been shown to have excellent protein-repellent ability to diminish bacterial adhesion[34,35]. Regarding the protein
repellent mechanism, it was suggested that MPC was highly hydrophilic, and there was an abundance of free water but no bound water in the hydrated MPC polymer. The presence of bound water caused protein adsorption. By contrast, the large amount of free water around the phosphorylcholine group was believed to detach proteins effectively, thereby repelling protein adsorption.

**ADHESIVE SYSTEM**

Adhesive system is a bridge between the dental tissue and resin restoration, thus, the use of antimicrobial primer and adhesive is a choice of the prevention of secondary caries. Moreover, adhesive containing quaternary ammonium antimicrobial monomer could kill residual bacteria quickly before curing, and play a role of pit and cavity disinfection. It had contact inhibitory effect against the bacteria after curing, and prevented bacteria from invading the deep dentin through bonding interface, thus reducing the prevalence of secondary caries and prolonging the service life of the restoration.

Accordingly, Zhang et al. had studied the effects of QADM and NAg incorporation to an adhesive system, Scotchbond Multi-Purpose (SBMP). It has been shown that adding QADM and NAg in both adhesive and primer had the strongest antimicrobial activity, while reducing metabolic activity, CFU, and lactic acid by an order of magnitude compared with control. And then, dimethylaminododecyl methacrylate (DMADDM), NAg, and NACP were incorporated into above adhesive system together and they found that modified bonding agent yielded potent and long lasting antimicrobial properties, and much stronger bond strength after 6 months of water aging than a commercial control. Meanwhile, 5 wt% DMADDM was incorporated into Clearfil SE Bond by Zhang et al. It had been observed that adhesives containing DMADDM inhibited the growth, lactic acid production, and Exopolysaccharides (EPS) metabolism of S. mutans biofilm at different stages, with no adverse effect on its dentin adhesive bond strength. However, owing to the special composition structure and non-toxic, no stimulation, cheap price and so on, DMADDM did not increase the cytotoxicity of SBMP adhesive system and without compromising the dentin bond strength. And then, they also incorporated DMADDM and NAg into above adhesive system for the first time, and got excellent antimicrobial property without compromising the dentin bond strength. Similarly, Sabatini et al. performed a study that incorporating of benzalkonium chloride (BAC) to an adhesive system which could protect hybrid layer, inhibit endogenous dentin proteolytic activity, reduce the degradation of collagen, and improve the bond strength.

**ACRYLIC RESIN**

Polymethyl methacrylate (PMMA) is one of the most commonly used restorative materials in oral clinical application. It has been used for years in different fields of dental medicine, including complete denture relining, orthodontic appliances, and maxillofacial plate etc. Further more, it has the advantages of convenient, non-toxic, no stimulation, cheap price and so on. However, owing to the special composition structure and characteristics of water absorption of PMMA materials, they are easy to be adhered by bacterial and fungal colonization, which is difficult to remove, thus causing the occurrence of dental caries, periodontal disease,
and denture stomatitis\textsuperscript{59,60}. Therefore, the research and development of antimicrobial PMMA are particularly important.

Accordingly, Pesci-Bardon et al.\textsuperscript{61,62} have performed a study that a quaternary ammonium compound was incorporated into an acrylic denture resin base in different concentrations, and the antimicrobial properties to \textit{Escherichia coli} (E. coli), \textit{Staphylococcus aureus} (S. aureus), \textit{Pseudomonas aeruginosa} (P. aeruginosa), and \textit{Candida albicans} (C. albicans) were tested. It was shown that 2\% quaternary ammonium compound polymerized with a denture acrylic resin displayed antimicrobial properties after a 4-week soaking period in artificial saliva. Besides that, Takahashi et al.\textsuperscript{53} had studied the effects of poly-2-methacryloxyethyl phosphorylcholine (PMPC) coated on the surface of acrylic resin and found that modified acrylic resin could prevent microbial retention.

### GLASS IONOMER CEMENT

Atraumatic restorative treatment (ART) is a method that can remove demineralized tooth tissues with hand instruments only and restore the prepared cavity and seal the adjacent pits and fissures with glass ionomer cement (GIC). This method has the characteristic of excellent adhesion, pressure resistance and wear resistance\textsuperscript{64-66}. GIC is a mixture of portland cement and modified poly carboxylic acid salt cement and integrates the advantages of both. Moreover, it has the characteristics of chemical bonding, good biocompatibility, chronic release of fluoride, and auxiliary mineralization and so on in the clinical practice\textsuperscript{65,67-70}. However, it is hard to remove bacteria by ART, and GIC does not possess antimicrobial activity, and the oral flora is complex, thus it is easy to cause secondary caries\textsuperscript{71,72}. Therefore, it is especially important that how to impart antimicrobial activity to GIC.

For these reasons, Dimkov et al.\textsuperscript{73} had incorporated BAC into the commercially available ChemFlex GIC in the following concentrations: 1, 2, and 3 wt\%, and they carried out an analysis of the release of chloride ion and fluoride ion in order to reflect the antimicrobial effect and fluoride releasing property of the GIC, respectively. Authors had observed that there were differences between the concentrations of chloride ion released, and there were no differences between the concentrations of fluoride released, by the samples with or without BAC. And then, CPC (1, 2 and 3 wt\%) and BAC (1, 2 and 3 wt\%) were added to ChemFlex and Fuji IX, respectively. It was observed that when the adding amount of the antimicrobial agents was 1 wt\%, the physical characteristics was the best through measurements of their setting times and determination of their compressive strength\textsuperscript{74}. In a similar study, Chlorhexidine diacetate (CHX) and cetrimide (CT) were added to Fuji IX at 1 and 2% w/w ratio by Deepalakshmi et al.\textsuperscript{87}. The results have shown that experimental Fuji IX containing CHX and CT were effective in inhibiting \textit{L.casei}, and incorporation of 1% CT was optimal to possess the appropriate antibacterial and physical properties by the agar diffusion test and the compressive strength\textsuperscript{75}. Besides that, the antibacterial activity, microhardness numbers (VHN), and cumulative fluoride releasing (CFR) patterns of conventional GICs (Fuji IX and Ketac Molar) containing CHX/CT (2.5/2.5\%) were evaluated by Tüzün et al.\textsuperscript{88}. The results showed that modified GICs had antibacterial effect to \textit{S.mutans} and \textit{L.casei}, and there were no significant differences for CFR between modified GICs and no modified GICs, but VHN decreased significantly for modified GICs\textsuperscript{89}. In addition, the conclusions of the research of Triolo were consistent with the above results\textsuperscript{77}.

### ENDODONTIC MATERIALS

Several studies have demonstrated that bacteria is the main factor to cause pulpal infection and periradicular lesion formation\textsuperscript{78-83}. Currently, most of the bacteria in the root canal can be cleaned by the method of mechanical chemistry to reduce the root canal infection, but there is still a small amount of residual bacteria in intercanal anastomoses, lateral branch of root canal, apical ramification, apical furcation and so forth. Furthermore, root canal instruments and flushing fluid are difficult to reach these areas. Therefore, it is impossible to remove the root canal infection completely\textsuperscript{82,83} and residual bacteria becomes a main risk factor for pulp infection and periradicular lesion\textsuperscript{84}. In conclusion, it is very important to use root canal filling materials which have the antibacterial and anti-biofilm characteristics, so as to eliminate the residual bacteria and prevent the infection of the root canal.

In this context, Gjorgievska et al.\textsuperscript{77} had studied the effects of BAC and CPC incorporation into the following endodontic sealers at 2% by mass: RoekoSeal, Endomethasone N, N2, Apexit Plus, and AH plus, regarding the antibacterial effect to \textit{S. mutans}, \textit{L. casei}, and \textit{A. viscosus}. It has been shown that antibacterial effect of short term of all the five modified endodontic sealers were improved, and Endomethasone N and N2 showed the most intensive antimicrobial activity among them, and the most susceptible microorganism was \textit{A. viscosus}. Besides that, Kesler et al.\textsuperscript{80} had introduced a low concentrations of insoluble antibacterial nanoparticles (IABN) as an attempt to improve the antibacterial effect of AH plus and GuttaFlow. The new materials, which were standard AH plus and GuttaFlow coated with IABN respectively, have demonstrated a significant and stable effect against \textit{Enterococcus faecalis} (E. faecalis). Similarly, in studies performed by Barros et al.\textsuperscript{89}, QPEI nanoparticles were incorporated into AH Plus and Pulp Canal Sealer EWT (PCS). The antibacterial effect against two \textit{E. faecalis} strains (ATCC and an endodontic isolate) were assessed, and results had shown that addition of QPEI nanoparticles improved the killing ability of PCS against biofilms of both \textit{E. faecalis} strains and the effects of AH Plus on the biomass of biofilms from the ATCC strain. Moreover, there were no relevant changes in physicochemical and
mechanical properties in PCS\(^{(90)}\). Besides, they had tested the biocompatibility of these new materials by comparing the cytotoxicity of QPEI with and without sealers on osteoblastic and osteoclastic cells, and from the results we could get the conclusion that the incorporation of 2\% QPEI particles into AH Plus and PCS modulates the proliferation and differentiation of bone cells, depending on the type of sealer and the cell, but without increasing the sealers’ cytotoxicity\(^{(91)}\). And then, CHX, CTR, or combination of both were added into AH Plus to confer it with bactericidal and anti-biofilm activity against \(E.\ faecalis\), and do not alter its physical properties\(^{(92,93)}\). Similarly, Gong \textit{et al.}\(^{(94)}\) had incorporated quaternary ammonium epoxy silicate (QAES) into epoxy resin-based AH Plus and had found that modified epoxy resin-based AH Plus might be a promising material for controlling endodontic infection at the time of canal filling and preventing subsequent reinfection. In addition, in a study performed by Kitagawa \textit{et al.}\(^{(95)}\), an experimental, chemically cured primer containing MDPB was prepared to develop a new resin-based root canal filling system. They found that this root canal filling system had the ability to disinfect the root canal effectively and was useful for achieving good sealing through study \textit{in vitro}, thus indicating its possible benefit for successful endodontic treatments.

### CONCLUSIONS

In this review, the antimicrobial effects, mechanical properties, and biocompatibilities of dental materials incorporated QACs were investigated, such as composite resin, adhesive system, acrylic resin, GIC, and endodontic materials (Table 1). However, the application of QACs are not limited to these. Several studies had incorporated QACs into bone cements\(^{(96)}\), titanium...

---

**Table 1 The application of QACs**

| QACs                                              | Abbreviation | Polymerizable or unpolymerizable | Application                                                |
|---------------------------------------------------|--------------|---------------------------------|-----------------------------------------------------------|
| 12-methacryloyloxydodecylpyridinium bromide        | MDPB         | polymerizable                    | endodontic materials\(^{(90)}\)                           |
| quaternary ammonium polyethyleneimine             | QPEI         | unpolymerizable                  | composite resin\(^{(46)}\), endodontic materials\(^{(90,91)}\) |
| quaternary ammonium dimethacrylate                 | QADM/IMQ     | polymerizable                    | composite resin\(^{(25,27,28)}\), adhesive system\(^{(32)}\) |
| 2-methacryloxylethyl dodecyl methyl ammonium bromide | MAE-DB       | polymerizable                    | composite resin\(^{(26,29)}\)                            |
| 2-methacryloxylethyl hexadecyl methyl ammonium bromide | MAE-HB       | polymerizable                    | composite resin\(^{(28,29)}\)                            |
| 2-dimethyl-2-dodecyl-1-methacryloxyethyl ammonium iodine | DDMAI       | polymerizable                    | composite resin\(^{(46)}\)                               |
| quaternary ammonium methacrylate                   | QAM          | polymerizable                    | composite resin\(^{(31)}\), adhesive system\(^{(53,54)}\) |
| 2-methacryloyloxyethyl phosphorylcholine            | MPC          | polymerizable                    | composite resin\(^{(31)}\)                               |
| dimethylaminododecyl methacrylate                  | DMADDM       | polymerizable                    | adhesive system\(^{(43-45)}\)                            |
| quaternary ammonium methacrylate polymer           | QAMP         | unpolymerizable                  | adhesive system\(^{(46-48)}\)                            |
| methacryloxylethyl cetyl ammonium chloride          | DMAE-CB      | polymerizable                    | adhesive system\(^{(49-52)}\)                            |
| benzalkonium chloride                               | BAC          | unpolymerizable                  | glass ionomer cement\(^{(75,76)}\), endodontic materials\(^{(87)}\) |
| poly-2-methacryloyloxyethyl phosphorylcholine       | PMPC         | unpolymerizable                  | acrylic resin\(^{(69)}\)                                 |
| cetylpyridinium chloride                            | CPC          | unpolymerizable                  | glass ionomer cement\(^{(76)}\), endodontic materials\(^{(87)}\) |
| cetrimide                                           | CT/CTR       | unpolymerizable                  | glass ionomer cement\(^{(75-77)}\), endodontic materials\(^{(87,93)}\) |
| quaternary ammonium epoxy silicate                 | QAES         | unpolymerizable                  | endodontic materials\(^{(46)}\)                          |
that application of QACs in dental materials is very promising. QACs have been also proved to be biocompatible with mammalian cells, thus suggesting that their application on dental materials do not represent a threat to human health. Generally speaking, however, with the increase of the amount of antibacterial agent, the mechanical properties and biocompatibility of the material will decrease. QACs belong to a kind of non-release antibiotic agent, and the antibacterial effect can be achieved when the dosage is relatively large. While the release antimicrobial agents can achieve better antibacterial effect at a low concentration, however, their extending antibacterial efficiency is low and they may be more toxic toward surrounding environments, the so-called “sudden release effect”. Therefore, we can develop a kind of control-release antibacterial agent with QACs as the carrier, which can achieve the ideal antibacterial effect with a small amount of additives, but has no influence on the mechanical properties and biocompatibility of the materials.

ACKNOWLEDGMENTS

Supported by Grant 81460107 from National Natural Science Foundation of China.

CONFLICTS OF INTEREST

The authors declare no competing financial interests.

REFERENCES

1) Buffet-Bataillon S, Tattevin P, Bonnaure-Mallet M, Jolivet-Gougeon A. Emergence of resistance to antibacterial agents: the role of quaternary ammonium compounds —a critical review. Int J Antimicrob Agents 2012; 39: 381-389.
2) Gilbert P, Moore L. Cationic antiseptics: diversity of action under a common epithet. J Appl Microbiol 2005; 99: 703-715.
3) Imazato S, Torii M, Tsuchitani Y, McCabe J, Russell R. Incorporation of bacterial inhibitor into resin composite. J Dent Res 1994; 73: 1437-1443.
4) Xiao YH, Chen JH, Fang M, Xing XD, Wang H, Wang YJ, Li F. Antibacterial effects of three experimental quaternary ammonium salt (QAS) monomers on bacteria associated with oral infections. J Oral Sci 2008; 50: 323-327.
5) Li F, Weir M, Xu H. Effects of quaternary ammonium chain length on antibacterial bonding agents. J Dent Res 2013; 92: 932-938.
6) Izuotani N, Imazato S, Nakajo K, Takahashi N, Takahashi Y, Ebisu S, Russell RR. Effects of the antibacterial monomer 1-methacryliclyoxyloxydodecylpyridinium bromide (MDPFB) on bacterial viability and metabolism. Eur J Oral Sci 2011; 119: 175-181.
7) Ma S, Izuotani N, Imazato S, Chen JH, Kiwa W, Yoshikawa R, Takeda K, Kitagawa H, Ebisu S. Assessment of bactericidal effects of quaternary ammonium-based antibacterial monomers in combination with colloidal platinum nanoparticles. Dent Mater J 2012; 31: 150-156.
8) Caillier L, de Givenchy ET, Levy R, Vandenbergh Y, Geribaldi S, Guittard F. Synthesis and antimicrobial properties of polymerizable quaternary ammoniums. Eur J Med Chem 2009; 44: 3201-3208.
9) Caillier L, de Givenchy ET, Levy R, Vandenbergh Y, Geribaldi S, Guittard F. Polymerizable semi-fluorinated gemini surfactants designed for antimicrobial materials. J Colloid Interface Sci 2009; 332: 201-207.
10) Huang L, Xiao YH, Xing XD, Li F, Ma S, Qi LL, Chen JH. Antibacterial activity and cytotoxicity of two novel cross-linking antibacterial monomers on oral pathogens. Arch Oral Biol 2011; 56: 367-373.
11) Antonucci JM, Zeiger DN, Tang K, Lin-Gibson S, Fowler BO, Lin NJ. Synthesis and characterization of dimethacrylates containing quaternary ammonium functional groups for dental applications. Dent Mater 2012; 28: 219-228.
12) Cheng L, Weir MD, Zhang K, Areola DD, Zhou X, Xu HH. Dental primer and adhesive containing a new antibacterial quaternary ammonium monomer dimethylaminododecyl methacrylate. J Dent 2013; 41: 345-355.
13) Stenger KJ, Lee J-J, Smith BD. Dramatic acceleration of the Menschutkin reaction and distortion of halide leaving-group order. J Org Chem 2007; 72: 9663-9668.
14) Melo MA, Guedes SF, Xu HH, Rodrigues LR. Nanotechnology-based restorative materials for dental caries management. Trends Biotechnol 2013; 31: 459-467.
15) Cenci M, Pereira-Cenci T, Cury J, Ten Cate J. Relationship between gap size and dentine secondary caries formation assessed in a microcosm biofilm model. Caries Res 2009; 43: 97-102.
16) Drumond JL. Degradation, fatigue, and failure of resin dental composite materials. J Dent Res 2008; 87: 710-719.
17) Ferracane JL. Resin composite —state of the art. Dent Mater 2011; 27: 29-38.
18) Samuel SP, Li S, Mukherjee I, Guo Y, Patel AC, Baran G, Wei Y. Mechanical properties of experimental dental composites containing a combination of mesoporous and nonporous spherical silica as fillers. Dent Mater 2009; 25: 296-301.
19) Papagiannoulis L, Kakaboura A, Eliades G. In vivo vs in vitro anticariogenic behavior of glass-ionomer and resin composite restorative materials. Dent Mater 2002; 18: 561-569.
20) Imazato S. Antibacterial properties of resin composites and dentin bonding systems. Dent Mater 2003; 19: 449-457.
21) Beyth N, Domb AJ, Weiss EL. An in vitro quantitative antibacterial analysis of amalgam and composite resins. J Dent 2007; 35: 201-206.
22) Kidd E, Toffenetti F, Mjör I. Secondary caries. Int Dent J 1992; 42: 127-138.
23) Li F, Weir MD, Chen J, Xu HH. Comparison of quaternary ammonium-containing with nano-silver-containing adhesive in antibacterial properties and cytotoxicity. Dent Mater 2013; 29: 450-461.
24) Beyth N, Rudovin-Farber I, Bahir R, Domb AJ, Weiss EL. Antibacterial activity of dental composites containing quaternary ammonium polyethyleneimine nanoparticles against Streptococcus mutans. Biomaterials 2006; 27: 3995-4002.
25) Cheng L, Weir MD, Xu HH, Antonucci JM, Kraigsley AM, Lin NJ, Lin-Gibson S, Zhou X. Antibacterial amorphous calcium phosphate nanocomposites with a quaternary ammonium dimethacrylate and silver nanoparticles. Dent Mater 2012; 28: 561-572.
26) Cheng L, Weir M, Zhang K, Xu S, Chen Q, Zhou X, Xu HH. Antibacterial nanocomposite with calcium phosphate and quaternary ammonium. J Dent Res 2012; 91: 460-466.
27) Cheng L, Weir MD, Zhang K, Wu EJ, Xu SM, Zhou X, Xu HH. Dental plaque microcosm biofilm behavior on calcium phosphate nanocomposite with quaternary ammonium. Dent Mater 2012; 28: 853-862.

28) Huang L, Sun X, Xiao YH, Dong Y, Tong ZC, Xing XD, Li F, Chai ZG, Chai YH. Antibacterial activity of a modified unfilled resin containing a novel polymerizable quaternary ammonium salt MAE-BH. Sci Rep 2016; 6: 33858.

29) He J, Söderling E, Lassila LV, Vallittu PK. Incorporation of an antibacterial and radiopaque monomer in to dental resin system. Dent Mater 2012; 28: e110-e117.

30) He J, Söderling E, Vallittu PK, Lassila LV. Investigation of double bond conversion, mechanical properties, and antibacterial activity of dental resins with different alkyl chain length quaternary ammonium methacrylate monomers (QAM). J Biomater Sci Polym Ed 2013; 24: 565-573.

31) Liang X, Söderling E, Liu F, He J, Lassila LV, Vallittu PK. Optimizing the concentration of quaternary ammonium dimethacrylate monomer in bis-GMA/TEGDMA dental resin system for antibacterial activity and mechanical properties. J Mater Sci Mater Med 2014; 25: 1387-1393.

32) Zhang N, Chen C, Melo MA, Bai YX, Cheng L, Xu HH. A novel protein-repellent dental composite containing 2-methacryloyloxyethyl phosphorylcholine. Int J Oral Sci 2015; 7: 103-109.

33) Ishiihara K, Nomura H, Miha H, Kuriita K, Iwasa K, Nakabayashi N. Why do phospholipid polymers reduce protein adsorption? J Biomed Mater Res 1998; 39: 323-330.

34) Sibarani J, Takai M, Ishihara K. Surface modification on microfluidic devices with 2-methacryloyloxyethyl phosphorylcholine polymers for reducing unfavorable protein adsorption. Colloids Surf B Biointerfaces 2007; 54: 88-93.

35) Kyomoto M, Mor Y, Miyahi F, Hashimoto M, Kawaguchi H, Takatori Y, Nakamura K, Ishihara K. Effects of mobility/immobility of surface modification by 2-methacryloyloxyethyl phosphorylcholine polymer on the durability of polyethylene for artificial joints. J Biomed Mater Res A 2009; 89A: 362-371.

36) Tateishi T, Kyomoto M, Kakinoki S, Yamaoka T, Ishiihara K. Reduced platelets and bacteria adhesion on poly(ether ether ketone) by photoinduced and self-initiated graft polymerization of 2-methacryloyloxyethyl phosphorylcholine. J Biomed Mater Res A 2014; 102: 1342-1349.

37) Sibarani J, Konno T, Takai M, Ishihara K. Photoinduced phospholipid polymer grafting on Parylene film: advanced lubrication and antibiofouling properties. Colloids Surf B Biointerfaces 2007; 54: 67-73.

38) Ishiihara K, Ueda T, Nakabayashi N. Preparation of phospholipid polymers and their properties as polymer hydrogel membranes. Polym J 1996; 22: 355-360.

39) Imazato S, Kaneko T, Takahashi Y, Noiri Y, Ebisu S. In vivo antibacterial effects of dentin primer incorporating MDFB. Oper Dent 2004; 29: 369-375.

40) Imazato S, Ma S, Chen JH, Xu HH. Therapeutic polymers for dental adhesives: loading resins with bio-active components. Dent Mater 2014; 30: 97-104.

41) Zhang K, Melo MAS, Cheng L, Weir MD, Bai Y, Xu HH. Effect of quaternary ammonium and silver nanoparticle-containing adhesives on dentin bond strength and dental plaque microcosm biofilms. Dent Mater 2012; 28: 842-852.

42) Zhang K, Cheng L, Wu EJ, Weir MD, Bai Y, Xu HH. Effect of water-ageing on dentin bond strength and antibiofilm activity of bonding agent containing new monomer dimethylaminododecyl methacrylate. J Dent 2013; 41: 504-513.

43) Zhang K, Wang S, Zhou X, Xu H, Weir M, Ge Y, Li M, Wang S, Li Y, Xu X, Zheng L, Cheng L. Effect of antibacterial dental adhesive on multispecies biofilms formation. J Dent Res 2015; 94: 622-629.

44) Wang S, Zhang K, Zhou X, Xu N, Xu HH, Weir MD, Ge Y, Wang S, Li M, Li Y, Xu C, Cheng L. Antibacterial effect of dental adhesive containing dimethylaminododecyl methacrylate on the development of Streptococcus mutans biofilm. Int J Mol Sci 2014; 15: 12791-12806.

45) Pupo YM, Farago PV, Nadal JM, Esmerino LA, Maluf DF, Zawadzki SF, Michél MD, dos Santos FA, Gomes OM, Gomes JC. An innovative quaternary ammonium methacrylate polymer can provide improved antimicrobial properties for a dental adhesive system. J Biomater Sci Polym Ed 2013; 24: 1443-1458.

46) Pupo YM, Farago PV, Nadal JM, Simão LC, Esmerino LA, Gomes OM, Gomes JC. Effect of a novel quaternary ammonium methacrylate polymer (QAMP) on adhesion and antibacterial properties of dental adhesives. Int J Mol Sci 2014; 15: 8908-9015.

47) Pupo YM, Farago PV, Nadal JM, Kovalik AC, dos Santos FA, Gomes OM, Gomes JC. Effect of antibacterial activity and bonding ability of an adhesive incorporating an antibacterial monomer DMAE-CB. J Biomed Mater Res B Appl Biomater 2009; 80: 813-817.

48) Li F, Chai Z, Sun M, Wang F, Ma S, Zhang L, Fang M, Chen JH. Anti-biofilm effect of dental adhesive with cationic monomer. J Dent Res 2009; 88: 372-376.

49) Li F, Chen J, Chai Z, Zhang L, Xiao Y, Fang M, Ma S. Effects of a dental adhesive incorporating antibacterial monomer on the growth, adherence and membrane integrity of Streptococcus mutans. J Dent 2009; 37: 269-296.

50) Chai Z, Li F, Fang M, Wang Y, Ma S. Antibacterial activity and bonding ability of an adhesive incorporating an antibacterial monomer DMAE-CB. J Biomed Mater Res 2009; 80: 813-817.

51) Li F, Weir MD, Chen J, Xu HH. Effect of charge density of binding agent containing a new quaternary ammonium methacrylate on antibacterial and bonding properties. Dent Mater 2014; 30: 433-441.

52) Zhou H, Li F, Weir MD, Xu HH. Dental plaque microcosm response to bonding agents containing quaternary ammonium methacrylates with different chain lengths and charge densities. J Dent 2013; 41: 1122-1131.

53) Sabatini C, Patel SK. Matrix metalloproteinase inhibitory properties of benzalkonium chloride stabilizes adhesive interfaces. Eur J Oral Sci 2013; 121: 610-616.

54) Sabatini C, Pashley DH. Aging of adhesive interfaces treated with benzalkonium chloride and benzalkonium methacrylate. Eur J Oral Sci 2015; 123: 102-107.

55) Sabatini C, Ortiz PA, Pashley DH. Preservation of resin-dentin interfaces treated with benzalkonium chloride adhesive blends. Eur J Oral Sci 2015; 123: 108-115.

56) Diaz-Arnold AM, Vargas MA, Shaull KL, Laffoon JE, Qian LA, Gomes OM, Gomes JC. Antibacterial properties of dental adhesives. Int J Mol Sci 2014; 15: 8908-9015.

57) Sabatini C, Ortiz PA, Pashley DH. Preservation of resin-dentin interfaces treated with benzalkonium chloride adhesive blends. Eur J Oral Sci 2015; 123: 108-115.

58) Diazen-Gonzalez LA, Vargas MA, Shaull KL, Laffoon JE, Qian F. Flexural and fatigue strengths of denture base resin. J Prosthodont Res 2015; 59: 258-262.

59) Wang S, Zhang K, Zhou X, Xu N, Xu HH, Weir MD, Ge Y. Antibacterial effect of dental adhesive containing dimethylaminododecyl methacrylate on the development of Streptococcus mutans biofilm. Int J Mol Sci 2014; 15: 12791-12806.

60) Pupo YM, Farago PV, Nadal JM, Esmerino LA, Maluf DF, Zawadzki SF, Michél MD, dos Santos FA, Gomes OM, Gomes JC. An innovative quaternary ammonium methacrylate polymer can provide improved antimicrobial properties for a dental adhesive system. J Biomater Sci Polym Ed 2013; 24: 1443-1458.
acrylic resin. Lett Appl Microbiol 2004; 39: 226-231.

62) Pesci-Bardon C, Fosse T, Sorre D, Madinier I. In vitro antiseptic properties of an ammonium compound combined with denture base acrylic resin. Gerodontology 2006; 23: 111-116.

63) Takahashi N, Iwasa F, Inoue Y, Morisaki H, Ishihara K, Baba K. Evaluation of the durability and antiadhesive action of 2-methacryloxyloxyethyl phosphorylcholine grafting on an acrylic resin denture base material. J Prosthet Dent 2014; 112: 194-203.

64) Frencken JE, Makoni F, Sithole WD. ART restorations and glass ionomer sealants in Zimbabwe: survival after 3 years. Community Dent Oral Epidemiol 1998; 26: 372-381.

65) Massara MdlLA, Alves J, Brandão P. Atraumatic restorative treatment: clinical, ultrastructural and chemical analysis. Caries Res 2002; 36: 430-436.

66) Frencken J, Van't Hof M, Van Amerongen W, Holmgren C. Effectiveness of single-surface ART restorations in the permanent dentition: a meta-analysis. J Dent Res 2004; 83: 120-123.

67) Taifour D, Frencken J, Beiruti N, Van't Hof M, Truin G. Effectiveness of glass-ionomer (ART) and amalgam restorations in the deciduous dentition: results after 3 years. Caries Res 2002; 36: 437-444.

68) Franci C, Deaton T, Arnold R, Swift E, Perdigao J, Bawden J. Fluoride release from restorative materials and its effects on dentin demineralization. J Dent Res 1999; 78: 1647-1654.

69) Smales RJ, Gao W. In vitro caries inhibition at the enamel.properties of conventional glass-ionomer cements containing chlorhexidine diacetate/cetrimide mixtures. J Esthet Restor Dent 2011; 23: 46-55.

70) Carvalho C, Bezerra A. Microbiological assessment of saliva from children subsequent to atraumatic restorative treatment (ART). Int J Paediatr Dent 2003; 13: 186-192.

71) Weerheijm KL, Groen HJ. The residual caries dilemma. Community Dent Oral Epidemiol 1999; 27: 436-441.

72) Weerheijm K, Kreulen C, de Soet J, Groen H, Van Amerongen W. Bacterial counts in carious dentine under restorations: 2-year in vivo effects. Caries Res 1999; 33: 130-134.

73) Dimkov A, Nicholson J, Gjorgievska E. On the possibility of incorporating antimicrobial components into glass-ionomer cements. Prilozi 2009; 30: 219-237.

74) Dimkov A, Nicholson W, Gjorgievska E, Booth S. Compressive strength and setting time determination of glass-ionomer cements incorporated with cetylpyridinium chloride and benzalkonium chloride. Prilozi 2011; 33: 243-263.

75) Deepalakshmi M, Poorni S, Miglani R, Rajamani I, göz A, Er K, Taşş. Properties of glass —Ionomer cements containing chlorhexidine and cetrimide: An in-vitro study. Indian J Dent Res 2010; 21: 552.

76) Tüzün R, Kusgöz A, Er K, Taşdemir T, Buruk K, Kemer B. Antibacterial activity and physical properties of conventional glass —Ionomer cements containing chlorhexidine diacetate/ cetrimide mixtures. J Esth Restor Dent 2011; 23: 46-55.

77) Triolo Jr PT. Commentary. antibacterial activity and physical properties of conventional glass-ionomer cements containing chlorhexidine diacetate/cetrimide mixtures. J Esth Restor Dent 2011; 23: 56.

78) Byström A, Sundqvist G. Bacteriologic evaluation of the efficacy of mechanical root canal instrumentation in endodontic therapy. Eur J Oral Sci 1981; 89: 321-328.

79) Fabricious L, Dahlen G, Öhman AE, Möller AJ. Predominant indigenous oral bacteria isolated from infected root canals after varied times of closure. Scand J Dent Res 1982; 90: 134-144.

80) Sundqvist G, Figdor D, Persson S, Sjögren U. Microbiologic analysis of teeth with failed endodontic treatment and the outcome of conservative re-treatment. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998; 85: 86-93.

81) Ricucci D, Siqueira JF. Biofilms and apical periodontitis: study of prevalence and association with clinical and histopathologic findings. J Endod 2010; 36: 1277-1288.

82) Paiva SS, Siqueira JF, Rôças JN, Carmo FL, Leite DC, Ferreira DC, Rachid CT, Rosado AS. Molecular microbiological evaluation of passive ultrasonic activation as a supplementary disinfecting step: a clinical study. J Endod 2013; 39: 190-194.

83) Rôças I, Lima K, Siqueira Jr J. Reduction in bacterial counts in infected root canals after rotary or hand nickel —titanium instrumentation — a clinical study. Int Endod J 2013; 46: 681-687.

84) Nair P, Henry S, Cano V, Vera J. Microbial status of apical root canal system of human mandibular first molars with primary apical periodontitis after “one-visit” endodontic treatment. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005; 99: 231-252.

85) Vera J, Siqueira JF, Ricucci D, Loghin S, Fernández N, Flores B, Cruz AG. One-versus two-visit endodontic treatment of teeth with apical periodontitis: a histobacteriologic study. J Endod 2012; 38: 1040-1052.

86) Ricucci D, Siqueira JF, Bate AL, Ford TRP. Histologic investigation of root canal–treated teeth with apical periodontitis: a retrospective study from twenty-four patients. J Endod 2009; 35: 493-502.

87) Gjorgievska E, Apostolska S, Dimkov A, Nicholson JW, Kafkazanjeva A. Incubation of antimicrobial agents can be used to enhance the antibacterial effect of endodontic sealers. Dent Mater 2013; 29: e29-e34.

88) Kesler Silvero D, Abramovitz I, Zaltsman N, Perez Davidi M, Weiss E, Borthy N. Towards antibacterial endodontic sealers using quaternary ammonium nanoparticles. Int Endod J 2013; 46: 747-754.

89) Barros J, Silva MG, Rôças JN, Gonçalves LS, Alves FF, Lopes MA, Pina-Vaz I, Siqueira JF Jr. Antibiofilm effects of endodontic sealers containing quaternary ammonium polyethyleneimine nanoparticles. J Endod 2014; 40: 1167-1171.

90) Barros J, Silva M, Rodrigues M, Alves F, Lopes M, Pina-Vaz I, Siqueira JF Jr. Antibacterial, physicochemical and mechanical properties of endodontic sealers containing quaternary ammonium polyethyleneimine nanoparticles. Int Endod J 2014; 47: 725-734.

91) Barros J, Costa-Rodrigues J, Lopes MA, Pina-Vaz I, Fernandes MH. Response of human osteoblastic and osteoclastic cells to AH plus and pulp canal sealer containing quaternary ammonium polyethyleneimine nanoparticles. J Endod 2014; 40: 1149-1155.

92) Bailón-Sánchez ME, Baca P, Ruiz-Linares M, Ferrer-Luque CM. Antibacterial and anti-biofilm activity of AH Plus with chlorhexidine and cetrimide. J Endod 2014; 40: 977-981.

93) Ruiz-Linares M, Bailón-Sánchez ME, Baca P, Valderrama M, Ferrer-Luque CM. Physical properties of AH Plus with chlorhexidine and cetrimide. J Endod 2013; 39: 1611-1614.

94) Gong SQ, Huang ZB, Shi W, Ma B, Tay FR, Zhou B. In vitro evaluation of antibacterial effect of AH Plus incorporated with quaternary ammonium epoxy silicate against Enterococcus faecalis. J Endod 2014; 40: 1611-1615.

95) Kitagawa R, Kitagawa H, Izutani N, Hirose N, Hayashi M, Imaizato S. Development of an antibacterial root canal filling material—SR Endoban. J Endod 2012; 38: 1040-1052.

96) Kaftandzieva A. Incorporation of antimicrobial agents can be used to enhance the antibacterial effect of endodontic sealers. Int Endod J 2014; 47: 725-734.

97) Barros J, Costa-Rodrigues J, Lopes MA, Pina-Vaz I, Siqueira JF Jr. Antibiofilm effects of endodontic sealers containing quaternary ammonium polyethyleneimine nanoparticles. J Endod 2014; 40: 1167-1171.

98) Ferrer-Luque CM. Antibactericidal and anti-biofilm activity of AH Plus with chlorhexidine and cetrimide. J Endod 2014; 40: 977-981.
98) Yang Y, Huang L, Dong Y, Zhang H, Zhou W, Ban J, Wei J, Liu Y, Gao J, Chen J. In vitro antibacterial activity of a novel resin-based pulp capping material containing the quaternary ammonium salt MAE-DB and Portland cement. PloS one 2014; 9: e112549.

99) Melo MA, Wu J, Weir MD, Xu HH. Novel antibacterial orthodontic cement containing quaternary ammonium monomer dimethylaminododecyl methacrylate. J Dent 2014; 42: 1193-1201.

100) Li F, Li F, Wu D, Ma S, Gao J, Li Y, Xiao Y, Chen J. The effect of an antibacterial monomer on the antibacterial activity and mechanical properties of a pit-and-fissure sealant. J Am Dent Assoc 2011; 142: 184-193.

101) Hirose N, Kitagawa R, Kitagawa H, Maezono H, Mine A, Hayashi M, Haapasalo M, Imazato S. Development of a cavity disinfectant containing antibacterial monomer MDPB. J Dent Res 2016; 95: 1487-1493.

102) Oguz Ahmet S, Mutluay MM, Seyfioglu Polat Z, Seseogullari Dirihan R, Bek B, Tezvergil-Mutluay A. Addition of benzalkonium chloride to self-adhesive resin-cements: some clinically relevant properties. Acta Odontol Scand 2014; 72: 831-838.

103) Korkmaz FM, Tüzün T, Baygin O, Buruk CK, Durkan R, Bagis B. Antibacterial activity, surface roughness, flexural strength, and solubility of conventional luting cements containing chlorhexidine diacetate/cetrimide mixtures. J Prosthet Dent 2013; 110: 107-115.

104) Kohnen W, Jansen B. Polymer materials for the prevention of catheter-related infections. Zentralbl Bakteriol 1995; 283: 1751-86.

105) Medlin J. Germ warfare. Environ Health Perspect 1997; 105: 290-292.

106) Nohr RS, Macdonald JG. New biomaterials through surface segregation phenomenon: new quaternary ammonium compounds as antibacterial agents. J Biomater Sci Polym Ed 1994; 5: 607-619.

107) Shearer AE, Paik JS, Hoover DG, Haynie SL, Kelley MJ. Potential of an antibacterial ultraviolet-irradiated nylon film. Biotechnol Bioeng 2000; 67: 141-146.