Review Article

Novel Protein-Repellent and Antibacterial Resins and Cements to Inhibit Lesions and Protect Teeth

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Orthodontic treatment is increasingly popular as people worldwide seek esthetics and better quality of life. In orthodontic treatment, complex appliances and retainers are placed in the patients’ mouths for at least one year, which often lead to biofilm plaque accumulation. This in turn increases the caries-inducing bacteria, decreases the pH of the retained plaque on an enamel surface, and causes white spot lesions (WSLs) in enamel. This article reviews the cutting-edge research on a new class of bioactive and therapeutic dental resins, cements, and adhesives that can inhibit biofilms and protect tooth structures. The novel approaches include the use of protein-repellent and anticaries polymeric dental cements containing 2-methacryloyloxyethyl phosphorylcholine (MPC) and dimethylaminododecyl methacrylate (DMAHDM); multifunctional resins that can inhibit enamel demineralization; protein-repellent and self-etching adhesives to greatly reduce oral biofilm growth; and novel polymethyl methacrylate resins to suppress oral biofilms and acid production. These new materials could reduce biofilm attachment, raise local biofilm pH, and facilitate the remineralization to protect the teeth. This novel class of dental resin with dual benefits of antibacterial and protein-repellent capabilities has the potential for a wide range of dental and biomedical applications to inhibit bacterial infection and protect the tissues.

1. Introduction

Orthodontic treatment is increasingly more popular as it can improve the facial esthetics, reduce the occurrence of dental diseases and injuries, enhance the oral functions, correct malocclusion, and minimize the psychosocial problems associated with poor dental and facial appearance. Complex appliances and retainers will be placed in the patients’ mouths for at least one year, which may facilitate the plaque aggregation despite good oral hygiene [1]. With the increase of plaque accumulation, the level of caries-inducing bacteria, especially Streptococcus mutans, is elevated, and the pH of the retained plaque on the enamel surface adjacent to the orthodontic brackets is decreased. This in turn hinders the remineralization process and causes decalcification [2–6]. The first clinical evidence of demineralization in tooth enamel is
seen as white spot lesions (WSLs), which are defined as the “subsurface enamel porosity from carious demineralization” that presents as “a milky white opacity” [1–3, 7–10]. The incidence of WSLs in fixed orthodontic treatments is as high as 60.9%, and the demineralization can become noticeable around the brackets as early as 4 weeks after the beginning of multibracket appliance treatment [1, 10].

Several methods were investigated to inhibit WSLs, such as educating and motivating the patient, mechanical plaque control and removal, modifying diet (low carbohydrate), and treating with topical fluoride [9–11]. However, these strategies require good long-term patient compliance and therefore are unreliable, especially in children and teenagers [11–13]. Consequently, novel preventive measures that do not rely on patient compliance need to be developed to prevent WSLs.

One promising approach is the development of antibacterial and protein-repellent materials [11, 14–17]. Quaternary ammonium methacrylates (QAMs) have been incorporated into dental resins to inhibit bacterial growth and plaque formation because of their excellent antibacterial potency [14–17]. Salivary proteins in the mouth can adhere to a clean polymer surface, providing anchor points for bacteria attachment, which is the first step in biofilm formation [18, 19]. Accordingly, efforts were made to develop novel protein-repellent dental materials to prevent the adsorption of proteins from the acquired pellicle [11, 20, 21]. Recently, protein-repellent dental cements, adhesives, and methacrylate resins were developed for the first time to repel bacterial adhesion, decrease acid production, and protect tooth structures. This article reviews the new generation of nanostructured, bioactive, and therapeutic dental materials with protein-repellent and anticaries properties.

2. Antibacterial and Protein-Repellent Orthodontic Cement to Inhibit WSLs

Fixed orthodontic appliances contribute to the adhesion of oral bacteria due to their complex design and irregular surfaces. These features limit the naturally occurring self-cleaning mechanisms and restrict proper preventive measures, thus resulting in enamel demineralization [1, 2]. Indeed, Lucchese and Gherlone [1] showed that the levels of acidogenic bacteria, such as Streptococcus mutans and lactobacilli, increased significantly in orthodontic patients, leading to WSLs around the orthodontic appliances. These lesions, which are characterized by their opacity, mineral loss, and decrease of fluorescence radiance, were commonly seen on the buccal surfaces of the teeth, around the brackets, especially in the gingival area [1, 2].

To effectively inhibit the prevalence of WSLs, the most important strategy is to prevent demineralization and biofilm formation [9]. Resin-modified glass ionomer cements (RMGIs) have been used for bracket-bonding cements due to their fluoride- (F-) releasing capabilities and acceptable bond strengths [11]. However, researchers found that RMGIs could accumulate more bacteria due to their relatively rough surfaces, high-surface free energy, and polarity [22, 23]. In addition, RMGIs were unable to change the low-pH environment, which hindered the remineralization

![Figure 1: Enamel shear bond strengths (SBS) (mean ± sd; n = 10). Incorporating 3% MPC+1.5% DMAHDM+0.1% NAg into VT did not adversely affect the SBS, compared to VT control (p > 0.1). Water aging for 30 d had no significant effect on SBS, compared to those at 1 d (p > 0.1). Bars with dissimilar letters indicate values that are significantly different from each other (p < 0.05). (Adapted from reference [38], with permission).](image-url)
plasmic leakage [15, 16, 28]. The antimicrobial mechanism
thus disrupting the bacterial membranes and causing cyto-


distilled water at 37°C (Figure 1) [38]. Figure 2 illustrates the
lactic acid results. VT with 1.5% DMAHDM alone reduced
the lactic acid production to about 1/5 that of VT control,
and VT with 0.1% NAg alone reduced to nearly 1/3. More
dramatically, VT with both DMAHDM and NAg reduced
the lactic acid production to 1/15 of that of VT control. A
similar trend was observed in the CFU and MTT
metabolic activity results, suggesting that DMAHDM and
NAg as dual antibacterial agents in RMGI had a multiply-
ing effect in reducing biofilm growth [38]. Representative
live/dead bacterial staining images are shown in
Figures 3(a)–3(d). VT control was covered with primarily
live bacteria (staining green) in Figure 3(a). As illustrated
in Figure 3(b), with the addition of MPC, the live bacteria
(staining green) were decreased but dead bacteria (staining
red) were not noticed, suggesting that MPC could repel
the bacteria adsorption but could not kill them. In
contrast, in Figure 3(c), VT+DMAHDM+NAg had much
more staining of compromised bacteria. In Figure 3(d),
VT+MPC+DMAHDM+NAg had the most red staining
and least green staining [38].

In addition, Zhang et al. [38] also found that VT with 3%
MPC+1.5% DMAHDM and VT with 3% MPC+0.1% NAg
had lower acid production than those using DMAHDM or
NAg without MPC. The acid production was the lowest in
VT+3% MPC+1.5% DMAHDM+0.1% NAg, which indicated
the synergistic effect of DMAHDM, NAg, and MPC in
biofilm inhibition.

These results are related to the mechanism of QAMs
and NAg to kill bacteria and the mechanism of MPC to
repel protein and bacteria adsorption. QAMs are consid-
ed to exhibit the


d_TMPC

of NAg was suggested to be Ag ions interacting with vital
enzymes of the bacteria, rendering DNA to lose its replica-
tion ability, thus leading to cell death [39–41]. Further-
more, studies indicated that NAg had a long distance
killing capability and relatively long-term antibacterial
activity [42].

The protein-repellent agent MPC is a methacrylate
with a phospholipid polar group in the side chain.
MPC has been shown to have excellent ability to repel
protein adsorption and prevent bacterial adhesion [20,
36]. The mechanism of protein repellency of MPC
relates to the structure of phospholipid which contains
a hydrophilic head (attracted to water) and hydrophobic
tails (repelled by water) [36, 37]. Phospholipids, a major
component of all cell membranes, can form lipid bi-
layers in which the nonpolar tail region faces the inner
area and the polar head region faces outward and in-
teracts. Therefore, the MPC polymers are hydrophilic
with an abundance of free water but no bound water
in the hydrated MPC polymer. While the presence of
bound water would cause protein adsorption, the large
amount of free water around the hydrated MPC polymer
is considered to detach proteins and repel protein
adsorption [36, 37, 43]. MPC can greatly reduce the
protein adsorption by maxing direct contacts between
bacteria and the polymer surface, thus enhancing the
antibacterial efficacy of DMAHDM and NAg. In return,
DMAHDM and NAg greatly reduces biofilm buildup
on the cement surface; this would help to expose more
MPC to repel proteins.

Furthermore, the use of triple agents may have a wide
applicability not only to dental cements but also to other
biomedical materials and tissue engineering scaffolds. The
protein–repellent and antibacterial combination could be
highly beneficial to inhibit biofilm growth and prevent infec-
tion in the wounds.
3. Multifunctional Cements to Protect Enamel from Demineralization

During orthodontic treatments, it is difficult to perform oral hygiene procedures on the bonded dental arches. Therefore, more bacteria are accumulated, which can lead to a decrease in pH that tips the demineralization-remineralization balance toward net mineral loss (demineralization) [2]. RMGIs are preferable to bond the brackets to the teeth because of F-releasing capability, which will reduce enamel demineralization [11, 44]. However, previous studies indicated that the initial F ion released form RMGIs was high and its concentration in the oral cavity was decreased rapidly over time due to salivary clearance and swallowing [45–48]. Moreover, the long-lasting low pH around the brackets restricted the remineralization process, so that more F ions could not produce a better cariostatic effect [24]. Therefore, a new bioactive orthodontic cement that could neutralize the acidic environment, alleviate subsurface enamel demineralization adjacent to brackets, and facilitate the remineralization effect would be highly desirable.

In a previous study, Ma et al. [44] developed a novel orthodontic cement containing protein-repellent MPC, antibacterial monomer DMAHDM, and remineralizing agent nanoparticles of amorphous calcium phosphate (NACP). They measured the average lesion depths (LD) via polarized light microscopy at three distance ranges: from 50 to 150 μm, from 150 to 250 μm, and from 250 to 350 μm, respectively. Among the four groups, the LD of group “RMGI+MPC+DMAHDM+NACP” was the least for all the three distance ranges (p < 0.05) [44]. The LD of Transbond XT control was the deepest for the three tested distance ranges (p < 0.05), which were 144.06 ± 24.59 μm, 148.24 ± 21.14 μm, and 157.51 ± 24.34 μm, respectively [44]. These results manifest that adhesives, which contain the NACP, do have the cariostatic effect. The results of enamel Knoop microhardness (KHN) also demonstrated the effect of preventing enamel demineralization by using NACP, MPC, and DMAHDM (Figure 4). “RMGI+MPC+DMAHDM+NACP” displayed the highest hardness from 25 to 175 μm deep at the three distances, which indicated that incorporating 3% MPC and 1.5% DMAHDM into RMGI could give the cement the ability of caries prevention close to the adhesive margin. The enamel hardness of novel cement with NACP was significantly greater than that without NACP; the novel cement with MPC, DMAHDM, and NACP exactly yielded significantly a better demineralization prevention effect when compared

![Figure 3: Representative live/dead staining images of 2-day biofilms grown on disks: (a) VT control, (b) VT with 3% MPC, (c) VT with 1.5% DMAHDM+0.1% NAg, and (d) VT with 3% MPC+1.5% DMAHDM+0.1% NAg. Live bacteria were stained green, and compromised bacteria were stained red. When live and dead bacteria were in close proximity or on the top of each other, the staining had yellow or orange colors. The VT with 3% MPC+1.5% DMAHDM+0.1% NAg had less bacterial adhesion, and the biofilms consisted of primarily compromised bacteria. (Adapted from reference [38], with permission).](image-url)
with a commercial RMGI control [44], Zhang et al. [49] also added MPC, DMAHDM, NAg, and NACP into RMGI and obtained similar conclusions. They studied the release of Ca and P ions at different NACP filler levels and different pH values. They found that the cement with NACP significantly increased the ion release with the increase of the NACP filler level and with the decrease of pH from 7 to 4 (p < 0.05) (Figure 5). These results demonstrate that NACP could release Ca and P ions at cariogenic pH when these ions are most needed to combat enamel demineralization [49].

Several studies showed that the NACP nanocomposite achieved Ca and P ion releases similar to those of traditional CaP composites, but the mechanical strength was at least twice as high [50, 51]. NACP composite could achieve high levels of Ca and P ions release at relatively low NACP filler levels because of the high surface area of the nanoparticles of 17.76 m²/g [50, 52]. Indeed, the enamel bond strength was not compromised even if the NACP filler level was 20% [49]. The pH was an important factor that affected the remineralization-remineralization balance. Takahashi and Nyvad [53] suggested that the de- and remineralization balance was tilted toward demineralization by the ecological phenomena from bacterial acid production. The bacterial acid-induced adaptation and selection within the microbiota, from the dynamic stability stage to the aciduric stage via the acidogenic stage, could change the environment form being relatively safe to being cariogenic [53–55]. It was suggested that the pH was lower than 4.5 in the plaque around the brackets [22, 56]. RMGI-containing NACP was shown to be a "smart material"; it could rapidly increase the Ca and P ion release at such a low pH and neutralize the acidic environment to a safe level of pH [49]. Therefore, adding NACP to RMGI delivered greater remineralization for enamel lesions than a fluoride-releasing commercial composite, increased the hardness back to normal, and inhibited or minimized WSLs [57]. A further study is still needed to investigate the cytotoxicity and biocompatibility of novel cement and to evaluate biofilm acid reduction and remineralization effects under clinically relevant in vivo conditions.

4. Bioactive Self-Etch Adhesive to Prevent Enamel Demineralization

Acid etch techniques are used routinely to bond orthodontic brackets to the teeth [58]. In 1955, Buonocore introduced the phosphoric acid etching technique which has revolutionized and improved the clinical practice of orthodontics [3, 59]. However, 37% phosphoric acid etching has several disadvantages, including causing enamel surface roughness, removing irreversibly several microns of the enamel layer, demineralization of the superficial layer of enamel near the brackets and junctions, and enamel fracture and crazing at the time of bracket debonding [58–60]. Indeed, Kim et al.
found that using acid etching could cause from 5 up to 10 mm of enamel loss, which could render the enamel surface more susceptible to demineralization during and after orthodontic treatment.

Several alternative approaches have been undertaken to reduce the adverse effects of the phosphoric acid etching, such as the use of different enamel preparation and adhesive systems [58]. Therefore, self-etching adhesive systems have been used for bracket bonding with the advantages of eliminating the need for a separate etching step, allowing for the simultaneous etching and adhesive penetration and forming a protective layer on the enamel surface. This avoids the negative effects of the traditional method with a separate acid etching step on enamel [61].

Adhesion of *S. mutans* to surfaces in the mouth will support the subsequent attachment and growth of other bacterial species, ultimately forming a microecosystem known as a biofilm [62]. At the tooth surface around the brackets, oral
biofilms can produce acids and cause WSLs or caries. Although dental plaque biofilm cannot be eliminated, it may be possible to reduce the pathogenic impact of the biofilm at the margin of the brackets by rendering the adhesive protein-repellent and antibacterial properties to suppress biofilm attachment and buildup [62]. It is highly desired to develop a new antibacterial self-etching adhesive to combat biofilms and WSLs.

In a previous study, Wang et al. [63] mixed MPC and DMAHDM into a self-etch adhesive (Adper Easy One, 3 M, St. Paul, MN, USA; referred to as AEO) to repel protein adsorption and decrease bacteria accumulation. In their study, the self-etch adhesive with 7.5% MPC had much less bacterial attachment and reduced the protein adsorption to only 5% that of control (Figure 6(a)). Adding either 5% DMAHDM or 7.5% MPC alone into AEO reduced the metabolic activity to nearly 17% and 33% of that of AEO control, respectively. More dramatically, biofilms on the adhesive containing both 7.5% MPC and 5% DMAHDM together had the lowest metabolic activity, which was only 5% of that of AEO control (Figure 6(b)) [63].

Based on these results, Wang et al. [63] suggested that there was a synergistic effect of MPC and DMAHDM in the adhesive on antiBiofilm properties. Quaternary ammonium compounds, which were positively charged, could bind to the negatively charged cell wall components, cause the leakage of the cytoplasmatic material, and finally lead to the lysis of the bacterial cells [31]. The antibacterial potency increased with increasing CL from 3 to 16 and decreased with CL further increasing to 18 [34]. DMAHDM with a chain length of 16 had the most potent antibacterial efficacy among all the QAMs tested [34]. The addition of MPC could dramatically enhance the antibacterial efficacy of DMAHDM by repelling the proteins on the adhesive resin to facilitate the mechanism of “contact killing” [64]. Therefore, the synergistic effect of MPC and DMAHDM was demonstrated not only in orthodontic cements but also in dental adhesives.

Another important issue is that an adequate bond strength is necessary for the fixed appliance therapy to be successful [61]. However, the bond strength also needs to be low enough to escape enamel damage during bracket debonding. Bishara et al. [59] suggest that enamel fracture and crazing existed at the time of bracket debonding, especially with ceramic brackets. As a result, orthodontists prefer bond failure at the bracket-adhesive interface to within the adhesive. Lamper et al. [65] found that, if the bond strength was lower than 12 MPa, little enamel damage was noticed; however, the risk would increase 14-fold if the strength was over 12 MPa. Reynolds et al. [66] suggested that the appropriate shear bonding strength for orthodontic cements was approximately 8 to 9 MPa, which was high enough to prevent the brackets from falling off the surface of the teeth, while avoiding enamel damage during the debonding process at the completion of the orthodontic treatment. The results of Wang et al. [63] showed that the enamel shear bond strength of the self-etch group containing MPC and DMAHDM was 9-10 MPa, which is clinically acceptable. Their research suggested that adding MPC and DMAHDM into the self-etch adhesive exhibited excellent antibacterial and protein-repellent effect without compromising the bond strength of the brackets.

5. Protein-Repellent and Antibacterial PMMA Resin to Suppress Biofilms

In addition to photopolymerization, heat cure is used in dentistry to increase the polymerization conversion and enhance the mechanical properties. Heat-cured resins are commonly used in orthodontics for making complicated functional appliances to correct severe skeletal class II and III malocclusions of preadolescent patients and for fabricating retainers to keep the esthetic results of orthodontic treatment [1, 67, 68]. The complex designing of appliances and retainers may prevent effective cleaning, thus inducing caries, periodontal diseases, and even denture-induced stomatitis in acrylic resin wearers [1, 69, 70]. Moreover, Takahashi et al. [21] suggested that polymethyl methacrylate- (PMMA-) based acrylic resins had a relatively high
water absorption capacity and were prone to dental plaque accumulation. Because the appliances and retainers would wear at least 2 years in the patient’s mouth, so the accumulation of biofilms and plaque on the resin surfaces could create unfavorable odors and further accelerate oral bacteria-related infection [67]. Although adequate cleaning of the appliances and retainers is imperative for the prevention of bacterial related diseases, it is more beneficial and necessary to develop an antibacterial resin surface. Antimicrobial agents were added into dental materials, which can be divided into two classes: released and nonreleased materials [31]. However, there were several disadvantages of using released antibacterial agents, including compromising mechanical properties of the carrier material over time, short-term effectiveness, and possible toxicity if the release was not properly controlled [71–73]. In contrast, polymeric antibacterial agents, which were nonvolatile and chemically stable, exhibited a stronger antimicrobial effect by interacting with and disrupting bacterial cell membranes [31, 74].

In another study, Cao et al. [75] combined MPC and DMAHDM into the PMMA-based acrylic resin to decrease the biofilm amounts and metabolic activity. The MPC mass fraction incorporated into acrylic resin was 3%, which was selected to produce the strongest protein repellency while not compromising the mechanical properties. Similarly, the maximum amount of DMAHDM in the PMMA resin was determined to be 1.5%. The flexural strength of the composite containing 3% MPC and 1.5% DMAHDM was 71 MPa, similar to 73 MPa of a commercial composite without antibacterial or protein-repellent functions (p > 0.1). The composite containing 3% MPC and 1.5% DMAHDM had an elastic modulus of 2020 MPa, similar to 2142 MPa of the commercial composite (p > 0.1) [75]. Using human saliva as inoculum, dental plaque microcosm biofilms were grown on the resins for two days to form a relatively mature biofilm. The representative live/dead staining photos of the 2-day biofilms on acrylic resins are illustrated in Figure 7. There were much less, but alive, bacteria via MPC (green staining) which reduced bacteria attachment by means of protein repellence, and there were substantial amounts of compromised bacteria (red staining) via DMAHDM which killed the bacteria by way of contact inhibition. Furthermore, the acrylic resin with 3% MPC+1.5% DMAHDM had the least bacterial adhesion, and the biofilms consisted of primarily dead bacteria with red staining, which demonstrated the enhanced antibacterial efficacy when double agents (protein-repellant MPC+antibacterial DMAHDM) were used in the same acrylate resin [75].

The new bioactive PMMA resin incorporating double agents of MPC and DMAHDM greatly reduced protein adsorption and biofilm growth, which could decrease the incidence of caries, periodontal diseases, and acrylic resin-related stomatitis. Their combined use may be beneficial not only to dental materials but also to other biomedical materials and tissue engineering fields, such as a bone cement.
in total joint arthroplasty, spinal surgery, fracture repair, and limb-sparing procedures [76]. Further investigations are needed to determine whether and how the strength and the capabilities of the antibiofilm and protein repel lence of the new PMMA resin would decrease after long-term aging in experiments simulating the oral environment.

6. Conclusions

This article represents a cutting edge review on the development of a new generation of antibacterial and protein-repellent dental cements and adhesives with bioactive and therapeutic properties to inhibit biofilms, promote remineralization, and protect the tooth structures. Compared with traditional materials, the new class of bioactive materials had excellent antibacterial and protein-repellent efficacy in various systems including orthodontic cements, self-etch adhesives, and polymethyl methacrylate resin-based appliances and retainers. These new materials incorporated novel agents, including antibacterial QAMs and NAg, protein-repellent agent MPC, and remineralization filler NACP. They inhibited oral bacterial pathogens, repelled protein adsorption, and promoted remineralization to effectively combat WSLs. This novel class of dental materials with antibacterial and protein-repellent activities provided the much-needed therapeutic capabilities that are lacking in traditional materials. These novel materials and methods are expected to have a wide range of applicability to other dental and biomedical materials to acquire antibacterial, protein-repellent, and therapeutic functions.

Disclosure

Li Cao, Junling Wu, and Qiang Zhang are co-first author.

Conflicts of Interest

The authors declare no conflict of interest.

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