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Therapeutic polymers for dental adhesives: Loading resins with bio-active components

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Abstract

Objectives—Many recent adhesives on the market exhibit reasonable clinical performance. Future innovations in adhesive materials should therefore seek out novel properties rather than simply modifying existing technologies. It is proposed that adhesive materials that are "bio-active" could contribute to better prognosis of restorative treatments.

Methods—This review examines the recent approaches used to achieve therapeutic polymers for dental adhesives by incorporating bio-active components. A strategy to maintain adhesive restorations is the focus of this paper.

Results—Major trials on therapeutic dental adhesives have looked at adding antibacterial activities or remineralization effects. Applications of antibacterial resin monomers based on quaternary ammonium compounds have received much research attention, and the loading of nano-sized bioactive particles or multiple ion-releasing glass fillers have been perceived as advantageous since they are not expected to influence the mechanical properties of the carrier polymer.

Significance—The therapeutic polymer approaches described here have the potential to provide clinical benefits. However, not many technological applications in this category have been successfully commercialized. Clinical evidence as well as further advancement of these technologies can be a driving force to make these new types of materials clinically available.

Keywords

Adhesives; Dental polymers; Bio-active; Antibacterial; Remineralization; QAC; Nano-particle

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1. Incorporation of QAC-based resin monomers

Quaternary ammonium compounds (QACs) are a group of cationic antimicrobials widely used for numerous industrial and pharmaceutical purposes [1]. In 1994, to develop non-agent-releasing antibacterial dental resins, Imazato et al. combined alkylpyridinium, a type of QAC, with a methacrylate group, and successfully synthesized a novel dental resin monomer, 12-methacryloyloxydodecylpyridinium bromide (MDPB) [2] (Fig. 1). While the QAC group is responsible for the antibacterial activity of MDPB, the methacrylate group allows for copolymerization with other conventional monomers. Since antibacterial monomers are immobilized in the resin matrix and do not leach out after curing, incorporating these monomers imposes no negative influences on the mechanical properties of the carrier material [2]. Without releasing these active agents, QAC-based resinous materials can exhibit stable and long-term antibacterial effects [2].

1.1. Antibacterial effects

Experimental antibacterial adhesive systems were first prepared by incorporating MDPB into the primer of commercial self-etching adhesive Liner Bond 2 [3]. Since then, the antibacterial activity of this prototype has been investigated and confirmed by a number of in vitro studies. Based on the findings of this experimental material, Clearfil Protect Bond, employing a 5% MDPB-containing primer, was developed and commercialized (sold as Clearfil SE Protect in USA and Clearfil Mega Bond FA in Japan).

Before curing, the MDPB-containing primer can kill bacteria rapidly because of the bactericidal activity of unpolymerized MDPB. It can thereby act as a cavity disinfectant. When the primer containing MDPB was kept in direct contact with planktonic bacteria, all bacteria were killed within 30 s [3–5]. It is noteworthy that the Clearfil Protect Bond primer was able to penetrate a 500-μm-thick dentin block [6] and eradicate caries-related species inside the dentin [7]. In vivo studies using beagle dogs found that the MDPB-containing primer could also inactivate *Streptococcus mutans* in the cavity [8]. Since residual bacteria are one of the primary causes of secondary caries, the cavity-disinfecting effects of the MDPB-containing primer may improve the outcomes of restorative treatments of caries lesions.

After curing, MDPB-containing resins can inhibit the growth of bacteria that comes into contact with the material, thereby acting as a so-called “contact inhibitor” (Fig. 2). When *S. mutans* was incubated in contact with the cured primer/adhesive surface containing MDPB, the number of viable bacteria was significantly reduced [9,10]. However, materials containing MDPB only exhibited bacteriostatic, rather than bactericidal effects, against the contacting bacteria. Two possible reasons for the reduction in antibacterial activity after curing have been proposed; (i) the movement of the immobilized molecules is limited, and (ii) the density of the QAC group of MDPB exposed on the outer surface is not high enough to kill bacterial cells.

MDPB-containing adhesives have been suggested to be effective in root caries arrestment and dental pulp preservation. This is attributed to their lesion-disinfecting effects and bacteriostatic functionality on contact with bacteria after curing. In a *S. mutans*-induced

artificial root caries model, a MDPB-containing adhesive completely prevents lesion progress [11]. As for pulp preservation, it has been confirmed using beagle dog models that the antibacterial primer containing MDPB can kill bacteria in the cavity, thus maintaining pulp vitality and primary odontoblastic function in infected, non-exposed and exposed cavities [8,12].

Besides MDPB, several other QAC monomers have been developed that can be utilized in resinous dental materials. Methacryloxylethyl cetyl dimethyl ammonium chloride (DMAE-CB, Fig. 3), synthesized by Chen's group, provided a commercial etch and rinse adhesive with stable antibacterial activities that does not damage the bonding capacity [13,14]. In recent years, significant efforts have been devoted to developing QAC monomers with improved properties. For instance, QAC monomers with two methacrylate groups have been synthesized to enhance the polymerization capacity [15–17] (Fig. 4). Antibacterial monomers with radio-opacity have also been developed using iodine as a counter ion [18,19] (Fig. 5).

1.2. Inhibitory effects against matrix metalloproteinases

Although modern adhesives can achieve satisfying immediate bonding to dentin, they demonstrate a loss of bond strength over time. Enzymatic degradation of the collagen matrix by host-derived matrix metalloproteinases (MMPs) plays a significant role in the destruction of the bonded interface [20]. One strategy to improve the durability of resin–dentin bonds is to use inhibitors that inactivate MMPs at the bonded interface [21]. Chlorhexidine has been found to be a non-specific MMPs inhibitor [22], and applying this agent to adhesives has been reported to be beneficial for the preservation of the resin–dentin bonds in vitro [23–25]. Similar to chlorhexidine, a QAC disinfectant of benzalkonium chloride effectively inhibited both soluble recombinant MMPs and matrix-bound dentin MMPs [26]. Tezvergil-Mutluay et al. speculated that QAC monomers may inhibit MMP activity. Using both soluble rhMMP-9 and matrix-bound endogenous MMPs, they found that QAC monomers, including MDPB, exhibited MMP inhibition behavior that was comparable to that of chlorhexidine [27]. Noticeably, MDPB at 5%, which is the concentration utilized for the primer of commercial adhesive Clearfil Protect Bond, achieved 89% inhibition of soluble rhMMP-9 and approximately 90% inhibition of matrix-bound MMPs. Compared with chlorhexidine or benzalkonium chloride, which may leach out from bonded interfaces over time, polymerizable MMP-inhibitors are advantageous as they can be retained in the hybrid layer for years by copolymerization. Several investigations into bond durability, including in vivo studies, revealed that the MDPB-containing adhesive produced a more durable interface than conventional adhesives [28,29]. Such improved durability achieved by MDPB-containing adhesives may be partially explained by the inhibitory effects of MDPB on MMPs.

2. Incorporation of nanoparticles

2.1. Antibacterial effects of silver nanoparticles

The antibacterial, antifungal, and antiviral actions of silver ions have been extensively investigated. Silver ions have been considered for applications as an antibacterial component

in resinous dental materials. However, polymers filled with silver ions typically release a burst of ions and lose their antibacterial activity within a short period [30]. Compared with free silver ions, reduced silver nanoparticles incorporated into a polymeric matrix provide a large reservoir of silver ions that can be released in a more controlled manner at a steady rate, allowing for long-term antibacterial effects [31]. The direct incorporation of silver nanoparticles into a polymer matrix is a common strategy for preparing antibacterial resinous materials [32]. However, silver nanoparticles are difficult to disperse, as nano-sized particles tend to aggregate. In 2011, a new technique for preparing dental polymers with evenly dispersed silver nanoparticles was described using coupling photo-initiated free radical polymerization of dimethacrylates with in situ silver ion reduction [33]. The experimental composites containing 0.08% of silver nanoparticles exhibited a 40% reduction in bacterial coverage [33].

As opposed to QAC monomer-containing resins whose bacteriostatic effects depend on the direct contact of bacteria with the material surface, resinous materials loaded with silver nanoparticles can inhibit bacteria on its surface as well as bacteria suspended in the culture medium away from the surface [34]. Therefore, QAC monomers and silver nanoparticles could show complimentary behavior for inhibiting bacteria. Experimental adhesives containing both QAC monomers and silver nanoparticles exhibited significantly enhanced antibacterial potency before and after curing compared with adhesives that used either agent alone [35–40].

2.2. Remineralization by calcium phosphate nanoparticles

To develop resinous materials with remineralization capabilities, calcium and phosphate ion-releasing fillers can be incorporated. The release and precipitation of calcium and phosphate can enhance the formation of hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$), which is the structural prototype for the major mineral component of teeth. In vitro studies revealed that methacrylate-based composites containing calcium phosphate fillers could release calcium and phosphate ions to supersaturated levels for apatite precipitation, and thus could effectively remineralize tooth lesions [41–44]. However, calcium phosphates containing resinous materials have the drawback of low mechanical strength. To develop experimental composites with high Ca and PO_4 release rates and with acceptable mechanical properties, Xu et al. combined nano-sized dicalcium phosphate anhydrous (DCPA) with silica-fused whiskers as co-fillers [45–48]. As the nanoparticles have a high surface area, high levels of Ca and PO_4 can be released with a relatively small amount of DCPA filler. This leaves room in the resin for a significant amount of silica-fused whiskers that can reinforce the mechanical properties. However, the silica-fused whisker-reinforced nanocomposite is relatively opaque with a whitish color owing to a refractive index mismatch between the whiskers and resin, and cannot be light-cured [49].

Amorphous calcium phosphate nanoparticles (NACP) were synthesized and combined with barium boroaluminosilicate glass particles, a typical dental glass filler similar to those in hybrid composites, to yield light-curable, weight-bearing, Ca and PO_4-releasing composites [50,51]. One advantage of the composites containing calcium phosphate fillers is that they are “smart” and could release relatively high amounts of Ca and PO_4 when the pH is

reduced from neutral to cariogenic of pH 4.0 [50]. Furthermore, these materials can rapidly neutralize the acidic medium, increasing the pH from 4.0 to 5.69 within 10 min [52]. The "smart" release of Ca and PO_4 as well as the neutralizing effects are promising material attributes to combat acid attack-induced mineral loss. A recent in vitro study using a 30-day demineralization/remineralization cyclic regimen found that NACP nano-composites could effectively remineralize the demineralized human enamel. These remineralization effects were 4-fold that of a commercial fluoride-releasing composite [53].

Based on these successful composites, Xu et al. conducted an approach to combine amorphous calcium phosphate with antibacterial components (QAC monomer or silver nanoparticles) (Fig. 6), and achieved a novel dental bonding agent with remineralization capacity and long-lasting antibacterial activity [54–57]. Such new materials having both remineralization and antibacterial properties may be of great benefit to preserve durable bonding interfaces and fight against secondary caries.

3. Application of a multiple ion-releasing glass filler

Pioneering work by Wilson and Kent suggests that the release of fluoride from glass-ionomer cements relies on the siliceous hydrogel layers on the surfaces of the glass particles. These layers result from the acid-base reaction between the ionleachable glass fillers and polyalkenoic acids [58]. Based on this theory, a revolutionary pre-reacted glass ionomer (PRG) filler, that are prepared by the acid-base reaction of fluoroboroaluminosilicate glass with polyalkenoic acid and added to resinous materials, has been introduced. Between the two types of fillers prepared, a full reaction type (F-PRG) and a surface reaction type (S-PRG) [59], the latter was found to be more useful because it is fabricated by the reaction limited to the glass surface and the mechanical properties of the core glass are not affected (Fig. 7). A ligand exchange mechanism within the pre-reacted hydrogel endows S-PRG fillers with the ability to release and recharge fluoride ions [60]. In addition, S-PRG fillers release multiple ions such as Sr^{2+}, Na^{+}, BO_3^{3-}, Al^{3+}, and SiO_3^{2-} at high concentrations [61] (Fig. 8). Several unique therapeutic effects are expected for resinous materials containing S-PRG fillers owing to the multiple ion-releasing capacity.

3.1. Promotion of calcification and remineralization

S-PRG fillers act in a quasi-intelligent way such that their release of fluoride is acidity-dependent. Their protective effects are then proportional to the threat being encountered [60]. The S-PRG filler can also achieve a sustained fluoride release owing to its fluoride recharging capacity [60,62–64]. Along with the release of multiple ions, S-PRG filler can modulate the pH of the surrounding medium, shifting the pH to neutral and weak alkaline regions [61]. Because of the released fluoride and silica, the eluate of resins filled with S-PRG fillers remarkably enhances the formation of apatite on phosvitinimmobilized agarose beads in the presence of a mineralizing solution [65]. It is well known that fluoride can improve the acid resistance of enamel and dentin by promoting the conversion of hydroxyapatite to fluoroapatite.

Sr released from S-PRG fillers may also enhance the acid resistance of teeth by converting hydroxyapatite to strontiumapatite [66,67]. In vitro studies have demonstrated that ions

released from the S-PRG filler-containing adhesive [68] or endodontic sealer [69] can be taken up by the enamel and dentin adjacent to the material, and the corresponding areas showed decreased demineralization following acid exposure. Similar results have also been reported for other S-PRG filler-containing materials, including proprietary materials such as orthodontic adhesive [70], fissure sealants [71], coating material [72], resinous vanish [73] and denture base resin [74].

3.2. Antibacterial effects/anti-plaque effects

There is increasing interest in the biological functions of the multiple ions released from S-PRG fillers, including the inhibitory effects on bacterial viability or activity. It was found that the S-PRG filler-containing resins, compared with conventional composites, significantly reduced the growth of *S. mutans* on their surfaces (unpublished data from Imazato's group). It was also reported that eluate from the S-PRG filler can suppress the adherence of *S. mutans* [75], and S-PRG filler-containing proprietary composites (Beautifil II) inhibited their adherence in the presence of saliva [76]. Further in vivo studies demonstrated that, after 8 h of intraoral exposure, a considerably lower quantity of dental plaque accumulated on the surface of Beautifil II [76]. Although the exact mechanism for the anti-plaque effects of the S-PRG filler is unknown, the release of multiple ions is believed to be related to this phenomenon.

Besides anti-plaque effects, S-PRG filler-containing proprietary resinous material inhibited bacteria-induced pH drop on the material surface, possibly due to the release of multiple ions [72]. Eluate from the S-PRG fillers exhibited inhibiting effects on the protease and gelatinase activities of *Porphyromonas gingivalis*. It also prevented the coaggregation between *P. gingivalis* and *Fusobacterium nucleatum* [75], indicating that these fillers may also be effective in combating periodontitis.

4. Addition of growth factors

Recently, in addition to conventional restorative treatments, resin adhesives have been attempted to be used for the adhesion of fractured roots, root-end filling, or sealing of perforations because they can provide a hermetic seal that prevents re-infections. In particular, several clinical studies reported the successful reconstruction of fractured roots with 4-META/MMA-based adhesive resin [77–79], which showed good bonding ability in a wet environment and high compatibility with osteoblasts or mesenchymal precursor cells [80,81]. However, none of the present adhesives available on the market promote tissue healing. Successful results cannot be expected when large bone defects exist adjacent to the sites that are repaired with adhesives.

To increase the success rate of these new treatment options and expand the use of resin adhesives, it is valuable to add the capacity to promote tissue regeneration. An effective, simple way to provide tissue regeneration abilities is to release growth factors from the adhesives. A number of studies on the local delivery of growth factors from dental implants to enhance osseointegration are available. For these studies, the use of fibroblast growth factor-2 (FGF-2) has been well documented. Utilization of polymer-based particle as a carrier to deliver FGF-2, such as poly(lactide-coglycolide) microspheres reported for

titanium implant [82], may be applied for resin-based restoratives. Few trials have been reported regarding the delivery of growth factors from dental resins. Attempts to fabricate FGF-2-releasing adhesives using drug carrier polymers are currently under investigation.

5. Concluding remarks

The approaches to achieve therapeutic polymers described here have the potential to contribute to successful restorative treatments. However, several points remain to be clarified to make these new types of materials clinically available. Researchers must show quantitative evidence that they have achieved appropriate kinetic control such that the bioactive elements will provide real benefits under in vivo conditions. For example, it is important to prove that the bioactive components are delivered at a rate and concentration to exhibit therapeutic effects regardless of shifts in environmental condition such as ionic concentrations, pH, or temperature. There also have been concerns about the potential toxicity of newly synthesized compounds. While the biocompatibility of the QAC-based monomer MDPB incorporated into the commercially available adhesive has been well documented [83], information to warrant the safety of other new compounds for clinical use needs to be collected. Since much attention has been paid on toxic effects of nanoparticles including those of silver [84,85] rigorous investigations on the risk of adverse health effects by usage of nanoparticles are required. Obviously, clinical evidence can be a key for commercialization of new technologies in this category.

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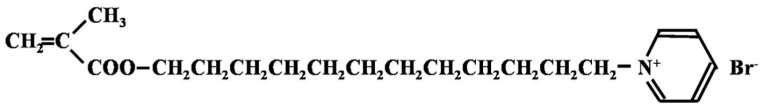

Fig. 1.
QAC-based antibacterial monomer MDPB.

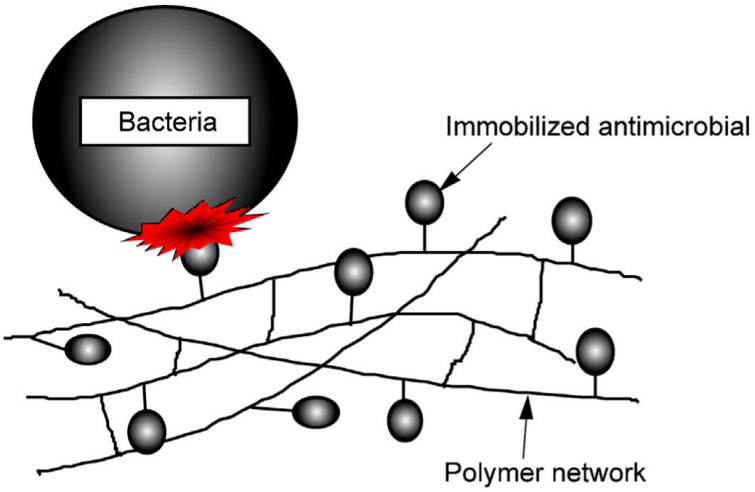

Fig. 2.

Antimicrobial immobilized in a polymer network by copolymerization of the antibacterial monomer with conventional methacrylate monomers; contact inhibition of bacteria.

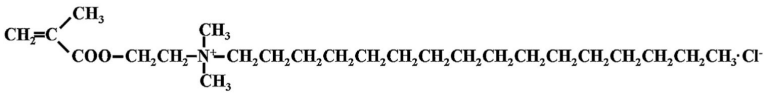

Fig. 3.
QAC-based monomer DMAE-CB.

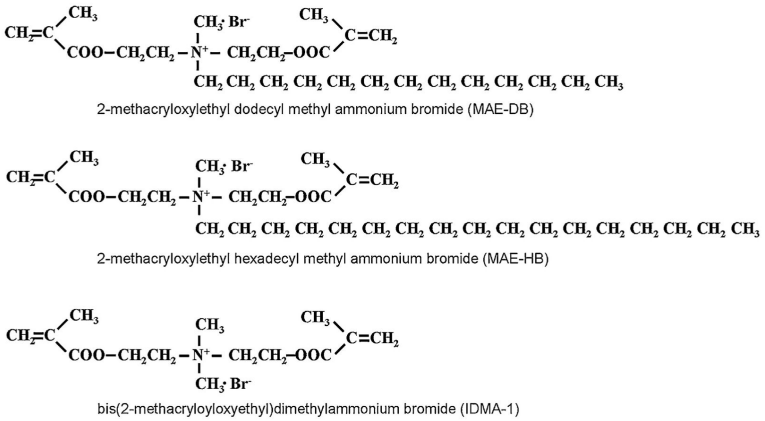

Fig. 4.
QAC-based monomers with two polymerizable groups.

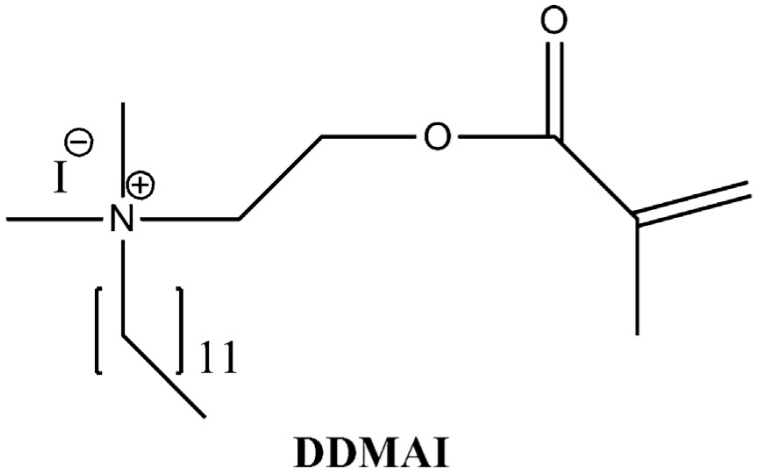

Fig. 5.
QAC monomer with iodine as a counter ion.

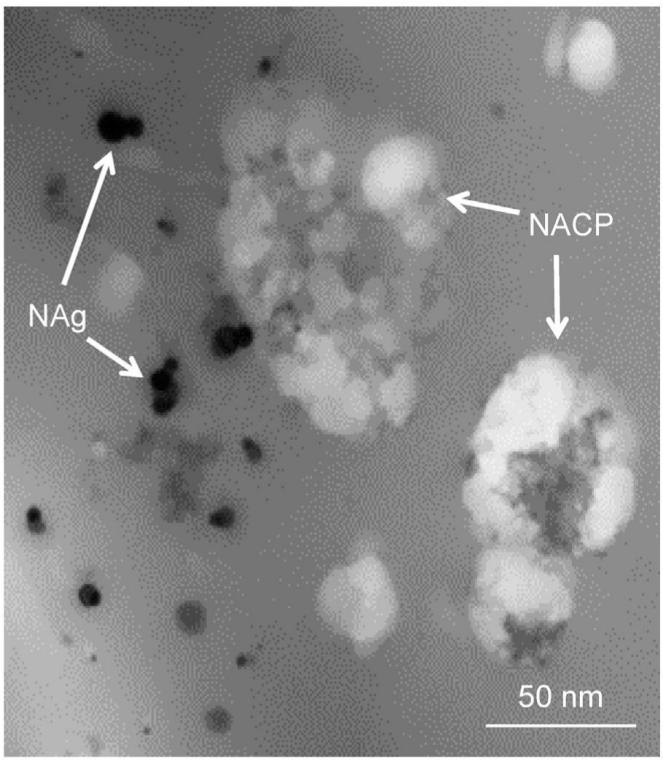

Fig. 6.
TEM image of amorphous calcium phosphate (NACP) and silver nanoparticles (NAg) incorporated in the adhesive resin.

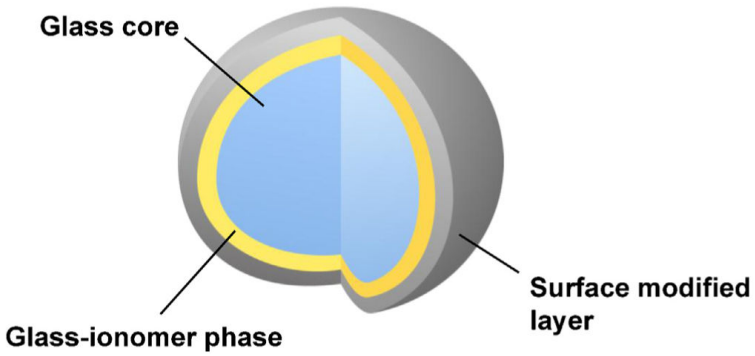

Fig. 7.
Structure of the surface pre-reacted glass-ionomer (S-PRG) filler.

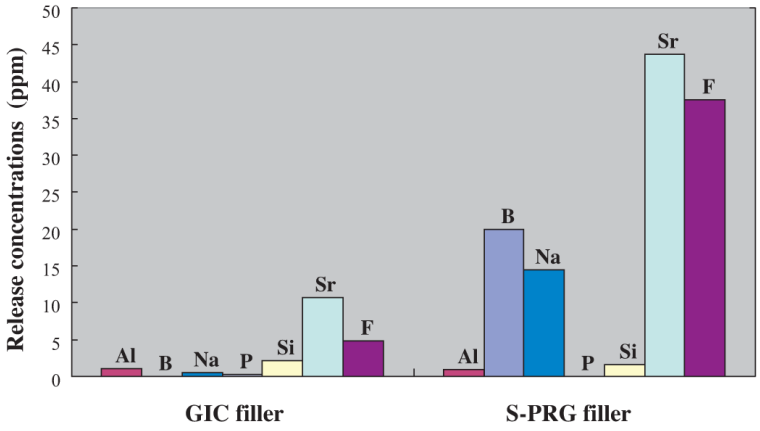

Fig. 8.

Concentration of ions released from conventional fluoroaluminosilicate glass of glass-ionomer cement (GIC filler) or S-PRG filler into distilled water after 24 h of immersion. Al, B, Na, P, Si, and Sr were detected by inductively coupled plasma atomic emission spectroscopy and F^{-} was measured using a fluoride electrode.