INTRODUCTION

The basic mechanical, physical, esthetic, and bonding properties of dental restorative/coating materials have greatly improved with technological developments, and the current materials on the market show excellent clinical performance. Therefore, the target of their advancement is shifting towards bio-active functionality to prevent primary/secondary diseases or promote tissue regeneration\(^1\),\(^2\). Several properties are considered to be useful bio-active functions for dental materials. These involve the addition of bio-protective effects, such as control of bacterial infection or strengthening of the tooth substrate, and the conferring of bio-promoting effects, such as remineralization, control of inflammation, or promotion of tissue regeneration\(^3\).

Incorporation of filler particles that release active components is a potential method to create bio-active materials, and many approaches are available to develop fillers with the ability to release components that provide “bio-protective” or “bio-promoting” properties; e.g. metal/calcium phosphate nanoparticles, multiple ion-releasing glass fillers, and non-biodegradable polymer particles. In this review paper, recent developments in cutting-edge filler technologies to release bio-active components are addressed and summarized according to their usefulness and functions, including control of bacterial infection, tooth strengthening, and promotion of tissue regeneration.

CONTROL OF BACTERIAL INFECTION

The control of bacterial infection to prevent disease is a popular function to be added to restorative/coating materials. One major approach that has been intensively investigated for resins is to immobilize antimicrobial components in/on the materials by incorporating a polymerizable bactericide such as quaternary ammonium compound (QAC)-based resin monomers. 12-methacryloyloxydodecylpyridinium bromide (MDPB), developed by Imazato et al.\(^7\),\(^8\), is representative of antibacterial QAC monomers\(^9\), and a prepolymerized resin filler with immobilized MDPB for resin composites has also been reported\(^9\). In current extensive studies, many kinds of QAC monomers, such as methacryloxylethyl cetyl dimethyl ammonium chloride (DMAE-CB)\(^10\), 2-methacryloyloxyethyl dodecyl methyl ammonium bromide (MAE-DB)\(^11\), bis(2-methacryloyloxyethyl) dimethylammonium bromide (IDMA-1)\(^12\), dimethylaminohexadecyl methacrylate (DMAHDM)\(^13\),\(^14\), 2-(methacryloyloxy)ethyl trimethylammonium chloride (MADQUAT)\(^15\), urethane dimethacrylates quaternary ammonium methacrylate (UDMQA)\(^16\),\(^17\), and quaternary ammonium bis-phenol A glycerolate dimethacrylate (QABGMA)\(^18\) have been developed. Moreover, the advancement of nanotechnology makes it possible to develop antibacterial dental resins with QAC-
functionalized nanofillers. Quaternary ammonium polyethylenimine (QPEI) and silica-based nanoparticles (QASi) have been reported as fillers of resin composites.\(^{19,20}\)

Another major approach to provide dental materials with bacterial-controlling effects is to apply a carrier for the delivery of antimicrobial components. Whereas the antibacterial effects of immobilized QAC depend on direct contact with bacteria, drug-release systems are effective in inhibiting bacteria not only on the surface but also at some distance away from the material (Fig. 1). However, a conventional approach to incorporating antimicrobial components directly into the materials limits the duration of the antimicrobial effects to a short period. Additionally, direct incorporation of additives compromises the physical properties of the materials and hampers their integrity for permanent restorations. Application of drug carriers such as filler particles is an effective way to overcome these problems, enabling long-lasting antimicrobial effects with less adverse influence on physical/mechanical properties.

**Metal nanoparticles**

Nanoparticles have been used to improve the polishability or gloss stability of restorative materials.\(^{3}\) According to ISO/TR 10993-22 and ISO/TR 80004-1, the nanoscale length range is approximately 1–100 nm, and nanoparticles are nano-objects with all external dimensions at the nanoscale. The high surface-area-to-volume ratio of nanoparticles offers high biological effectiveness at low concentrations. Metals have been used for centuries as antimicrobial agents, and the use of metal nanoparticles composed of silver, copper, zinc oxide, titanium dioxide, and platinum as fillers with antimicrobial effects has been reported.\(^{21-24}\)

Silver has antibacterial, antifungal and antiviral activity. Silver ions strongly interact with thiol groups of vital enzymes and inactivate them, causing DNA to lose the ability to replicate and leading to cell death. Therefore, silver ions have been incorporated into resinous materials to provide antimicrobial effects. However, this method does not provide continuous delivery of silver ions. Compared with free silver ions, silver nanoparticles incorporated into a polymeric matrix work as a large reservoir of silver ions that can be released in a controlled manner at a steady rate, allowing for long-term antibacterial effects.\(^{28}\)

The direct incorporation of silver nanoparticles into a polymer matrix is a common method of preparing antibacterial resinous materials.\(^{29}\) However, silver nanoparticles are difficult to disperse, since nano-sized particles tend to aggregate and agglomerate. To prevent the aggregation, silver nanoparticles are stabilized by various functional groups on their surface using coating agents or stabilizers such as polymers, polysaccharides, or citrates.\(^{30,31}\)

Another unique approach to avoid aggregation in resinous materials is a technique for preparing dental polymers with evenly dispersed silver nanoparticles using coupling photo-initiated free radical polymerization of dimethacrylates with \textit{in situ} silver ion reduction\(^{32}\) (Fig. 2). Experimental composites containing 0.08% silver nanoparticles exhibited a 40% reduction in bacterial coverage.\(^{32}\) The antibacterial activity of the nanocomposites is thought to be due to the release of silver ions from the nanoparticles. As opposed to QAC monomer-containing resins whose inhibitory effects

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**Fig. 1** Antimicrobial properties conferred by contact inhibition of immobilized bactericide (A) and controlled release of antimicrobial components (B).

**Fig. 2** Transmission electron microscope image of silver nanoparticles dispersed in Bis-GMA/TEGDMA resin. The silver nanoparticles appear as black dots (arrow).
depend on contact inhibition of bacteria, resinous material incorporating silver nanoparticles can inhibit bacteria suspended in culture medium as well as on its surface\(^3\) (Fig. 1). Therefore, QAC monomers and silver nanoparticles could show complementary behavior for inhibiting bacteria. Experimental adhesives or endodontic resin-based sealers containing dual agents composed of QAC monomers and silver nanoparticles significantly enhanced antibacterial potency before and after curing compared with those using either agent alone\(^34,35\).

Although silver nanoparticle fillers in resinous materials exhibited strong antimicrobial effects, the color of the resin become darker due to the plasmon effect of the particles. It has been argued that this discoloration of resinous materials is a significant problem in an esthetic region. Therefore, other antibacterial nanoparticles have been used as fillers for resinous materials. Zinc oxide powders, incorporated as opaque reinforcing fillers in resin composites\(^36\), display antimicrobial properties by blocking the synthesis of bacterial cell walls\(^6,37\). Zinc acts directly by altering cell proteins via processes such as transmembrane proton translocation, or indirectly by inhibiting protease-induced bacterial adhesion\(^37-39\). Sevinç and Hanley\(^22\) reported that zinc oxide nanoparticles blended as a 10% (w/w) fraction into resin composites reduced the growth of *Streptococcus sobrinus* biofilm by 80% compared with unmodified composites. Nanoparticles composed of zinc are expected to exhibit antibacterial effects with less influence on the esthetic properties of restorative materials compared with silver nanoparticles.

**Ion-releasing glass fillers: single ion-releasing type**

Hench *et al.* developed a so-called bioactive glass composed of SiO\(_2\), Na\(_2\)O, CaO, and P\(_2\)O\(_5\), designated as bioglass 45S5 and commercially known as Bioglass\(^65,40\). This glass is a potential candidate for use as filler particles in restorative materials, because it enhances hard tissue regeneration and exerts some antimicrobial effects by releasing ions\(^41,42\). Its antimicrobial effects are attributed to the release of ions such as calcium ions, which cause neutralization of the local acidic environment and lead to a local increase in pH that is not well tolerated by bacteria\(^42,43\). Khvostenko *et al.*\(^44\) reported that resin composites containing another type of bioglass (65S) reduced bacterial penetration into the marginal gaps of simulated tooth restorations. Davis *et al.*\(^45\) developed glass fillers containing calcium and fluoride prepared by the sol-gel method. It was shown that resin composites incorporating these fillers acted as a single source of both calcium (Ca\(^{2+}\)) and fluoride (F\(^-\)) ions in aqueous solutions, and that the composites could be readily recharged with F\(^-\). However, because the effective concentration of Ca\(^{2+}\) and F\(^-\) ions against microorganisms is so high, the antimicrobial effects of a local increase in pH due to calcium ions from bioglass 45S5 or 65S or the release of fluoride ions from fluoride-containing glass fillers are limited\(^46\). As a result, additional components are needed to more effectively demonstrate antibacterial effects against oral microorganisms.

**Ion-releasing glass fillers: multiple ions-releasing type**

Recently, much attention has been paid to glass fillers that show diverse effects by releasing multiple ions. BioUnion filler (Fig. 3) is a glass powder composed of SiO\(_2\), ZnO, CaO, and F, and can be categorized as a bio-functional multi-ion-releasing filler. These glass particles have a silicon-based glass structure and are capable of releasing zinc (Zn\(^{2+}\)), Ca\(^{2+}\), and F\(^-\) (Fig. 4). A tooth surface coating composed of BioUnion fillers (Caredyne-Shield, GC, Tokyo, Japan) and a dental cement for root surface...
restoration containing BioUnion fillers (Caredyne-Restore, GC) have been commercialized.

Zn$^{2+}$ is known to exhibit antibacterial effects against oral bacteria$^{37,46}$. The MIC/MBC values of zinc against $S$. mutans were reported to be lower than those of fluoride$^{6}$. Interestingly, Liu et al.$^{6}$ reported that BioUnion fillers demonstrated accelerated release of Zn$^{2+}$ under acidic conditions and exerted strong bactericidal or inhibitory effects against oral bacteria. Once dental plaque is formed on the surface of teeth or materials, the pH values in the area are decreased by acids produced from oral bacteria such as $S$. mutans. When these acidogenic bacteria produce acids, BioUnion fillers incorporated into materials are capable of effectively releasing Zn$^{2+}$. Such acidity-induced release of Zn$^{2+}$ has the potential to effectively hinder plaque formation on the surface of materials (Fig. 5).

A surface pre-reacted glass-ionomer (S-PRG) filler is another technology of interest that releases multiple ions$^{5}$. This filler is prepared via an acid-base reaction between fluoroboroaluminosilicate glass and a polyacrylic acid. The pre-reacted glass-ionomer phase on the surface of the glass core allows S-PRG filler to release and recharge F$^{-}$,$^{47,48}$ Moreover, S-PRG filler releases aluminum (Al$^{3+}$), borate (BO$_3^{3-}$), sodium (Na$^{+}$), silicate (SiO$_3^{2-}$), and strontium (Sr$^{2+}$) ions from the fluoroboroaluminosilicate glass core (Fig. 6). Several studies have demonstrated that resin composites containing S-PRG fillers exhibit antibacterial effects against oral bacteria$^{49,50}$. Miki et al.$^{49}$ examined the inhibitory effects of experimental resin composites containing different ratios of S-PRG fillers on $S$. mutans growth, and found that the specimens containing S-PRG filler at 13.9 (vol)% or greater inhibited bacterial growth on their surfaces. They further demonstrated that the inhibitory effects shown by the experimental resin composites were mainly attributed to release of BO$_3^{3-}$ and F$^{-}$. It was also reported that eluate from the S-PRG filler suppressed the adherence of $S$. mutans$^{50}$, and thus $S$. mutans biofilm formation could be inhibited on the surface of resin composites containing S-PRG fillers (Fig. 7). Further in vivo studies demonstrated that commercially available resin composites containing S-PRG fillers (Beautifil II, Shofu, Kyoto, Japan) significantly inhibited dental plaque accumulation on their surface after intraoral exposure for 24 h compared with control composites without S-PRG fillers$^{50}$ (Fig. 8).

Recent investigation of the association of the eluate from S-PRG filler with bacterial metabolism by Kitagawa et al.$^{52}$ revealed that $S$. mutans glucose metabolism and acid production could be inhibited by low concentrations of BO$_3^{3-}$ or F$^{-}$ at which bacterial growth was not affected. Nomura et al.$^{53}$ reported that the eluate from S-PRG fillers effectively inhibited $S$. mutans growth through downregulation of operons related to $S$. mutans sugar metabolism, resulting in attenuation of the cariogenicity

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**Fig. 5** Acidity-induced release of zinc ions from BioUnion filler.

**Fig. 6** Structure of S-PRG filler and release of multiple ions.
of *S. mutans*. Indeed, a coating resin containing S-PRG fillers (PRG Barrier Coat, Shofu), which produces a coating layer with a thickness of approximately 200 µm, inhibited the fall in pH induced by glucose consumption by *S. mutans* on the material surface54).

Ion release from S-PRG fillers is effective in suppressing the activity of periodontal pathogens. The eluate of S-PRG fillers shows inhibitory effects on the protease and gelatinase activity of *Porphyromonas gingivalis*53). Using animal studies, Iwamatsu-Kobayashi et al.55) reported that the eluate from S-PRG fillers demonstrated preventive effects against tissue destruction in periodontal disease. It was also found that the coaggregation of *P. gingivalis* and *Fusobacterium nucleatum* could be prevented in the presence of S-PRG filler eluate51), indicating that the release of ions may contribute to the prevention of periodontitis.

**Polymer particles as a reservoir of antimicrobials**

Another approach to providing restorative materials with long-lasting antimicrobial effects is to apply non-biodegradable polymer particles as a reservoir of antimicrobials2). Imazato et al. developed non-biodegradable polymer particles made of hydrophilic monomer 2-hydroxyethyl methacrylate (HEMA) and a cross-linking monomer trimethylolpropane trimethacrylate (TMPT)2) (Fig. 9). Cetylpyridinium chloride (CPC), a QAC, was loaded into these polymer particles by two different methods60). One method was to immerse the particles into a CPC aqueous solution to uptake CPC. The other method was to add CPC powder to the HEMA/TMPT monomer mixture and cure it to produce polymers. Using the immersion method, it was found that the polymer particles consisting of 50% HEMA/50% TMPT were useful for loading and release of CPC. Using the pre-mixing method, there was a marked extension of the release period compared with that of the immersion method. The CPC-pre-mixed polymer particles achieved a longer period of CPC-release over 120 days, and demonstrated antimicrobial effects against oral bacteria. Moreover, the combination of pre-mix loading of CPC powder and recharging using a CPC solution was effective in achieving persistent antimicrobial effects with sustained release of CPC.

Application of the polyHEMA/TMPT particles loaded with CPC to resin-based endodontic sealers or denture
bases/crowns promises to increase the effectiveness of treatments by conferring properties that inhibit bacterial infection².

**TOOTH STRENGTHENING**

The effects of fluoride, calcium and phosphate ions on promoting mineralization and improving the acid resistance of enamel and dentin have been reported. Ion-releasing materials have the potential to inhibit demineralization and enhance remineralization of teeth, leading to cessation or prevention of caries.

_Calcium phosphate fillers/nanoparticles_

Amorphous calcium phosphate (ACP) can release calcium and phosphate ions that are favorable for tooth mineralization. _In vitro_ studies revealed that resin composites containing calcium phosphate fillers could release calcium and phosphate ions to supersaturated levels for apatite precipitation on enamel⁵⁷-⁵⁹. However, the incorporation of ACP decreased the flexural strength of resin composites to about half that of unfilled resin⁵⁸. Such a low strength was inadequate to make these composites acceptable as restorative materials⁶⁰.

To develop experimental composites with the ability to release high concentrations of calcium and phosphate ions and with acceptable mechanical properties, Xu _et al._ combined nano-sized dicalcium phosphate anhydrous (DCPA) with silica-fused whiskers as co-fillers⁶¹-⁶⁴. With the high surface area of nanoparticles, large amounts of calcium and phosphate ions can be released from a small number of particles. This leaves room in the resin composite for a significant amount of silica-fused whiskers to reinforce the mechanical properties. However, silica-fused whisker-reinforced nanocomposite is relatively opaque with a whitish color owing to a refractive index mismatch between the whiskers and the resin, and cannot be light-cured⁶⁵. To solve these problems, nanoparticles of amorphous calcium phosphate (NACP; diameter=116 nm) were synthesized _via_ a spray-drying technique⁶⁶,⁶⁷. The boroaluminosilicate glass particles were combined with NACP to yield light-curable and weight-bearing particles, and experimental composites incorporating these fillers were prepared. One advantage of the calcium phosphate fillers is that they promote the release of Ca²⁺ and phosphate ions (PO₄³⁻) under acidic conditions (pH 4.0)⁶⁸, and then rapidly neutralize the acids from pH 4.0 to 5.69 within 10 min⁶⁹. These effects combat acidity-induced mineral loss. In addition, NACP-containing resin composites are capable of effectively remineralizing demineralized human enamel after a 30-day demineralization/remineralization cycle⁷⁰. The remineralization effects were 4-fold stronger than those of a commercial fluoride-releasing composite. Furthermore, Xu _et al._ conducted an approach to combine ACP with antibacterial components (QAC monomer and/or silver nanoparticles), and created a novel dental bonding agent with remineralization capacity and long-lasting antibacterial activity⁷⁰-⁷³. Such new materials having both remineralization and antibacterial properties may be of great benefit to prevent secondary caries.

_Ion-releasing glass fillers_

Bioglass 45S5, developed by Hench in 1969, can bind to hard tissues and stimulate tissue mineralization⁴⁰, showing the ability to remineralize enamel and dentin⁷⁴,⁷⁵. The adhesion of resin-modified glass ionomer to dentin has also been shown to be enhanced by bioglass 45S5 application⁷⁶. A resin adhesive containing bioglass 45S5 improves the nano-mechanical properties of demineralized dentin⁷⁷. The incorporation of bioglass 65S into a dentin desensitizer can reduce fluid flow in dentinal tubules, resulting in reduced dentinal hypersensitivity⁷⁸. Jang _et al._⁷⁹ revealed that the incorporation of 65S significantly increased the micro-hardness of the adjacent demineralized dentin, and calcium phosphate peaks on the dentin could be detected by attenuated total reflection Fourier-transform infrared spectroscopy (ATR-FTIR) analysis. These findings suggest that resin composites containing 65S can remineralize adjacent demineralized dentin.

_S-PRG fillers modulate the pH of the surrounding_
medium and shift the pH to neutral and weak alkaline regions\(^8^9\). The release of fluoride and silica from resins incorporating S-PRG fillers promotes apatite formation on phosphitin-immobilized agarose beads in the presence of a mineralizing solution\(^8^0\). Fluoride can also improve the acid resistance of the tooth substrate through the formation of fluoroapatite. In vitro studies have demonstrated that ions released from S-PRG filler-containing adhesive\(^8^0\) or endodontic sealer\(^9^0\) 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 such as orthodontic adhesives\(^8^3\), fissure sealants\(^8^4\), coating materials\(^8^5,8^6\), resinous vanishes\(^8^7\) and denture base resins\(^8^8\). Uo et al.\(^8^8\) investigated the local structure of strontium taken up by teeth using X-ray absorption fine structure analysis, and revealed that the strontium content in enamel and dentin was 100 times greater after immersion in the eluate of S-PRG filler than before immersion. It is known that strontium enhances the acid resistance of teeth by converting hydroxyapatite to strontiumapatite\(^8^9,9^0\). The structure of Sr in the enamel and dentin after immersion in the eluate of S-PRG filler was similar to that of synthetic Sr incorporated into hydroxyapatite. The Sr released from S-PRG filler would be incorporated into the Ca site of hydroxyapatite. Thus, Sr incorporated into hydroxyapatite may improve the acid resistance and remineralization of enamel and dentin.

BioUnion filler exhibits not only antibacterial effects but also inhibition of demineralization and enhancement of remineralization in tooth structure\(^9^1\). Zinc demonstrates an inhibitory effect against demineralization of enamel\(^9^2\) and dentin\(^9^3\), and inhibits the activity of matrix metalloproteinase (MMP)\(^9^4\). It is well known that F\(^-\) and Ca\(^2+\) released from BioUnion filler inhibit demineralization and enhance remineralization of teeth\(^9^5,9^6\). Cement containing BioUnion filler (Caredyne-Restore) exhibited superior enhancement of root dentin remineralization when compared with conventional glass ionomer cement and resin composite (Fig. 10).

**PROMOTION OF TISSUE REGENERATION**

Although extensive research on tissue regeneration is being undertaken in a variety of medical fields, there are few studies investigating fillers for dental materials with the ability to promote tissue regeneration. Several studies have revealed that active components incorporated into inorganic or resin cements promote tissue formation or regeneration as well as cell proliferation and differentiation.

**Ion-releasing glass fillers**

Strontium is known to promote osteogenic differentiation of mesenchymal stem cells and suppress the activity of osteoclasts\(^9^7\). The administration of strontium has been shown to increase bone density and decrease the incidence of fractures in vertebral and peripheral bones\(^9^8\). Sasaki et al.\(^9^9\) fabricated strontium-doped glass that was incorporated into glass ionomer cements. These experimental cements promoted the alkaline phosphatase activity of osteoblasts without the need for any media supplements for osteoblastic differentiation.

Apart from its anti-plaque and remineralization effects, S-PRG filler has the ability to promote tertiary dentinogenesis. Experimental cements as pulp capping materials were prepared by mixing S-PRG fillers with copolymers of acrylic acid and tricarboxylic acid. After pulp exposure in rat molars, the experimental cement exhibited complete tertiary dentin formation at 2 and 4 weeks due to the release of multiple ions such as Sr\(^2+\), BO\(_3^{3-}\), F\(^-\), or SiO\(_2^{2-}\). Okamoto et al.\(^1^0^0\) reported that S-PRG cement regulated the expression of genes related to osteo/dentinogenic differentiation. CXCL-12 and TGF-\(\beta\) were upregulated following ion release from S-PRG filler and may contribute to tertiary dentin formation during the healing process in pulpal tissue.

**Polymer particles as a reservoir of antimicrobials**

The non-biodegradable polyHEMA/TMPT particles described before can also act as a carrier for growth factors. Takeda et al.\(^1^0^1\) reported that fibroblast growth factor-2 (FGF-2) could be loaded into polymer particles composed of 90 (wt%) HEMA and 10 (wt%) TMPT, and FGF-2 adsorbed to the particles was released over 14 days and maintained its activity in increasing the proliferation of osteoblast-like cells. Additionally, when the FGF-2-loaded polymer particles were
incorporated into 4-META/MMA-based adhesive resin, the experimental resin released FGF-2 for 14 days. Such sustained release of FGF-2 from the experimental resin promoted cell proliferation (Fig. 11), and induced bone regeneration of rat calvaria implanted with experimental resin incorporating polymer particles. This finding suggests that adhesive resins incorporating FGF-2-loaded polymer particles could be applied to root-end fillings, perforation sealing, or the repair of fractured roots in cases with severely damaged periodontal tissue.

CONCLUSIONS

The filler technologies to create “bio-active” materials described here have great potential to contribute to successful restorative and preventive treatments. Many of these materials demonstrate possible benefits in vitro or under clinically-relevant experimental conditions. New generation materials with “bio-active” functions, including commercially available materials that contain BioUnion filler or S-PRG filler, require further intensive research to show that they can provide substantial benefits in clinical settings. For such purposes, it is meaningful to develop convenient in vitro evaluation systems that are specifically designed for “bio-active” materials, with realistic simulations of the oral environment.

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REFERENCES

1) Imazato S, Ma S, Chen JH, Xu HHK. Therapeutic polymers for dental adhesives: Loading resins with bio-active components. Dent Mater 2014; 30: 97-104.
2) Imazato S, Kitagawa H, Tsutsumi R, Thongthai P, Sasaki J, Kitagawa R. Non-biodegradable polymer particles for drug delivery: A new technology for “bio-active” restorative materials. Dent Mater J 2017; 36: 524-532.
3) Schmalz G, Hickel R, van Landuyt KL, Reichl FX. Nanoparticles in dentistry. Dent Mater 2017; 33: 1298-1314.
4) Zhang K, Baras B, Lynch CD, Weir MD, Melo MAS, Li Y, et al. Developing a new generation of therapeutic dental polymers to inhibit oral biofilms and protect teeth. Materials 2018; 11: 1-17.
5) Lizzi F, Villat C, Attik N, Jackson P, Grosgeorget B, Goutaudier C. Mechanical characteristic and biological behaviour of implanted and restorative bioglasses used in medicine and dentistry: A systematic review. Dent Mater 2017; 33: 702-712.
6) Liu Y, Kohno T, Tsutsumi R, Kitagawa H, Imazato S. Acidity-induced release of zinc ion from BioUnion filler and its inhibitory effects against Streptococcus mutans. Dent Mater J 2020 (in press).
7) Imazato S. Bio-active restorative materials with antibacterial effects: new dimension of innovation in restorative dentistry. Dent Mater J 2009; 28: 11-19.
8) Imazato S, Torii M, Tsuitakabeya Y, McCabe JF, Russell RRB. Incorporation of bacterial inhibitor into resin composite. J Dent Res 1994; 73: 1437-1443.
9) Imazato S, Ebi N, Takahashi Y, Kaneko T, Ebisu S, Russell RRB. Antibacterial activity of bactericide-immobilized filler for resin-based restoratives. Biomaterials 2003; 24: 3605-3609.
10) Xiao YH, Ma S, Chen JH, Chai ZG, Li F, Wang YJ. Antibacterial activity and bonding ability of an adhesive incorporating an antibacterial monomer DMAE-CB. J Biomed Mater Res B Appl Biomater 2009; 80 B: 813-817.
11) Jiao Y, Niu LN, Ma S, Li J, Tay FR, Chen JH. Quaternary ammonium-based biomedical materials: state-of-the-art, toxicological aspects and antimicrobial resistance. Prog Polym Sci 2017; 71: 53-90.
12) Antonucci JM, Zeiger DN, Tang K, Lim-Gibson S, Fowler BO, Lin NJ. Synthesis and characterization of dimethacrylates containing quaternary ammonium functionalities for dental applications. Dent Mater 2012; 28: 219-228.
13) Zhang N, Zhang K, Xie X, Dai Z, Zhao Z, Imazato S, et al. Nanostructured polymeric materials with protein-repellent and anti-caries properties for dental applications. Nanomaterials 2018; 8: 393.
14) Cheng L, Zhang K, Zhang N, Melo MAS, Weir MD, Zhou XD, et al. Developing a new generation of antimicrobial and bioactive dental resins. J Dent Res 2017; 96: 855-863.
15) Nascimento PL de MM, Meevis CTW, Maske TT, Ogliari FA, Cenci MS, Pfeifer CS, et al. Addition of ammonium-based methacrylates to an experimental dental adhesive for bonding metal brackets: curious lesion development and bond strength after cariogenic challenge. Am J Orthod Dentof Orthop 2017; 151: 949-956.
16) Liang X, Huang Q, Liu F, He J, Lin Z. Synthesis of novel antibacterial monomers (UDMQA) and their potential application in dental resin. J Appl Polym Sci 2013; 129: 3373-3381.
17) Huang Q, Huang S, Liang X, Qin W, Liu F, Lin Z, et al. The antibacterial, cytotoxic, and flexural properties of a composite resin containing a quaternary ammonium monomer. J Prosthet Dent 2018; 120: 609-616.
18) Makvandi P, Ghaemy M, Mohseni M. Synthesis and characterization of photo-curable bis-quaternary ammonium dimethacrylate with antimicrobial activity for dental restoration materials. Eur Polym J 2016; 74: 91-90.
19) Béthyl N, Yudovin-Farber I, Perez-David d, M. Domb AJ, Weiss EL. Polyethyleneimine nanoparticles incorporated into resin composite cause cell death and trigger biofilm stress in vivo. Proc Natl Acad Sci 2010; 107: 22038-22043.
20) Zaltsman N, Ionescu AC, Weiss EI. Surface-modified nanoparticles as anti-biofilm filler for dental polymers. PLoS One 2017; 12: 1-18.
21) Gutiérrez MF, Malasqui P, Matos TP, Sáez A, Souza S, Bermudez J, et al. Mechanical and microbiological properties and drug release modeling of an etch-and-rinse adhesive containing copper nanoparticles. Dent Mater 2017; 33: 309-320.
22) Seving BA, Hanley L. Antibacterial activity of dental composites containing zinc oxide nanoparticles. J Biomed Mater Res B Appl Biomater 2010; 94B: 22-31.
23) Totu EE, Nechifor AC, Nechifor G, Aboul-Enein HY, Cristache CM. Poly(methyl methacrylate) with TiO 2 composites containing zinc oxide nanoparticles. J Biomed Mater Res 2010; 94B: 22-31.
24) Hashimoto M, Honda Y. Effect of nanoparticles on biofilm growth disruption: silver and platinum nanoparticles with an identical capping agent. Nano Biomed Mater 2018; 10: 61-68.
25) Allaker RP. Critical review in oral biology & medicine: the use of nanoparticles to control oral biofilm formation. J Dent Res 2010; 89: 1175-1186.
26) Morones JR, Eleshiguerra JL, Camacho A, Holt K, Kouri JB, Ramirez JT, et al. The bactericidal effect of silver nanoparticles. Nanotechnology 2005; 16: 2346-2353.
27) Hoskins JS, Karanfil T, Serkiz SM. Removal and sequestration of iodide using silver-impregnated activated carbon. Environ Sci Technol 2002; 36: 784-789.
28) Dam M, Münstedt H, Rösch A. Long-term antimicrobial polyamide 6/silver-nanocomposites. J Mater Sci 2007; 42: 6067-6073.
29) Kassaei MZ, Akhavan A, Sheikh N, Sadogar A. Antibacterial effects of a new dental acrylic resin containing silver nanoparticles. J Appl Polym Sci 2008; 110: 1609-1703.
30) Zhang C, Hu Z, Deng B. Silver nanoparticles in aquatic environments: physicochemical behavior and antimicrobial mechanisms. Water Res 2016; 88: 403-427.
31) Hashimoto M, Yanagiuchi H, Kitagawa H, Yamaguchi S, Honda Y, Imazato S. Effect of metal nanoparticles on biofilm formation of Streptococcus mutans. Nano Biomed 2017; 9: 61-68.
32) Cheng YJ, Zeiger DN, Howarter JA, Zhang X, Lin NJ, Antonucci JM, et al. In situ formation of silver nanoparticles in photocrosslinking polymers. J Biomed Mater Res B Appl Biomater 2011; 97B: 124-131.
33) Li F, Weir MD, Chen J, Xu HHK. Comparison of quaternary ammonium-containing with nano-silver-containing adhesive in antibacterial properties and cytotoxicity. Dent Mater 2013; 29: 450-461.
34) Zhang K, Li F, Imazato S, Cheng L, Liu H, Arola DD, et al. Dual antibacterial agents of nano-silver and 12-methacryloyloxydodecylypyridinium bromide in dental adhesive to inhibit caries. J Biomed Mater Res B Appl Biomater 2013; 101B: 929-938.
35) Baras BH, Melo MAS, Sun J, Oates TW, Weir MD, Xie X, et al. Novel endodontic sealer with dual strategies of dimethylaminohecadecyl methacrylate and nanoparticles of silver to inhibit root canal biofilms. Dent Mater 2019; 35: 1117-1129.
36) Bowen RL, Cleek GW. A new series of X-ray-opaque reinforcing fillers for composite materials. J Dent Res 1972; 81: 1577-182.
37) He G, Pearce EIF, Sissons CH. Inhibitory effect of ZnCl2 on glycolysis in human oral microbes. Arch Oral Biol 2002; 47: 117-129.
38) Cummins D. Zinc citrate/Triolosan: a new anti-plaque system for the control of plaque and the prevention of gingivitis: short-term clinical and mode of action studies. J Clin Periodontol 1991; 18: 455-461.
39) Gin G, Cao H, Qiao Y, Meng F, Zhu H, Liu X. Osteogenic activity and antibacterial effect of zinc ion implanted titanium. Colloids Surf B Biointerfaces 2014; 117: 158-165.
40) Hencz LL. The story of Bioglass®. J Mater Sci Mater Med 2006; 17: 967-978.
41) Tezvergil-Murthuay A, Sessegullari-Dirihan R, Feitosa VP, Cama G, Brauer DS, Sauro S. Effects of composites containing bioactive glasses on demineralized dentin. J Dent Res 2017; 96: 999-1005.
42) Gubler M, Stark WJ, Zehnder M, Waltimo T, Sener B, Brunner TJ. Do bioactive glasses convey a disinfecting mechanism beyond a mere increase in pH? Int Endod J 2008; 41: 670-678.
43) Galarraga-Vinueza ME, Mesquita-Guimaraes J, Magini RS, Souza JCM, Fredel MC, Becaccini AR. Anti-biofilm properties of bioactive glasses embedding organic active compounds. J Biomed Mater Res A 2017; 105: 672-679.
44) Khvostenko D, Hilton TJ, Ferracane JL, Mitchell JC, Kruzic JJ. Bioactive glass fillers reduce bacterial penetration into marginal gaps for composite restorations. Dent Mater 2016; 32: 73-81.
45) Davis HB, Gwinner F, Mitchell JC, Ferracane JL. Ion release from, and fluoride recharge of a composite with a fluoride-containing bioactive glass. Dent Mater 2014; 30: 1187-1194.
46) Gu H, Ling J, Zhou X, Liu L, Zhao Z, Gao JL. Mineralising and antibacterial properties of novel endodontic sealer. J Biomed Mater Res B Appl Biomater 2018; 101B: 929-938.
47) Hashimoto M, Yanagiuchi H, Kitagawa H, Yamaguchi S, Honda Y, Imazato S. Effect of metal nanoparticles on biofilm formation of Streptococcus mutans. Nano Biomed 2017; 9: 61-68.
neutralizing properties and bacteria inhibition of amorphous calcium phosphate dental nanocomposite. J Biomed Mater Res B Appl Biomater 2011; 98B: 80-88.

69) Weir MD, Chow LC, Xu HHK. Remineralization of demineralized enamel via calcium phosphate nanocomposite. J Dent Res 2012; 91: 979-984.

70) Cheng L, Weir MD, Xu HHK, Antonucci JM, Lin NJ, Lin-Gibson S, et al. Effect of amorphous calcium phosphate and silver nanocomposites on dental plaque microcosm biofilms. J Biomed Mater Res B Appl Biomater 2012; 100B: 1378-1386.

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

72) Melo MAS, Cheng L, Weir MD, Hsia RC, Rodrigues LKA, Xu HHK. Novel dental adhesive containing antibacterial agents and calcium phosphate nanoparticles. J Biomed Mater Res B Appl Biomater 2013; 101B: 620-629.

73) Melo MAS, Cheng L, Zhang K, Weir MD, Rodrigues LKA, Xu HHK. Novel dental adhesives containing nanoparticles of silver and amorphous calcium phosphate. Dent Mater 2013; 29: 199-210.
demineralization effect of a novel fluoride-releasing varnish on dentin. Am J Dent 2012; 25: 347-350.
87) Mukai Y, Kamiyo K, Fujino F, Hirata Y, Teranaka T, Ten Cate JM. Effect of denture base-resin with prereacted glass-ionomer filler on dentin demineralization. Eur J Oral Sci 2009; 117: 750-754.
88) Uo M, Wada T, Asakura K. Structural analysis of strontium in human teeth treated with surface pre-reacted glass-ionomer filler eluate by using extended X-ray absorption fine structure analysis. Dent Mater J 2017; 36: 214-221.
89) Featherstone JDB, Shields CP, Khademazad B, Oldershaw MD. Acid reactivity of carbonated apatites with strontium and fluoride substitutions. J Dent Res 1983; 62: 1049-1053.
90) Dedhiya MG, Young F, Higuchi WI. Mechanism for the retardation of the acid dissolution rate of hydroxyapatite by strontium. J Dent Res 1973; 52: 1097-1109.
91) Takahashi K, Shimada Y, Togami J, Yoshiyama M. The effects of root demineralization inhibition by a glass ionomer cement containing zinc glass. Jpn J Conserv Dent 2019; 62: 190-198.
92) Mohammed NR, Mneimne M, Hill RG, Al-Jawad M, Lynch RJM, Anderson P. Physical chemical effects of zinc on in vitro enamel demineralization. J Dent 2014; 42: 1096-1104.
93) Takatsuka T, Tanaka K, Iijima Y. Inhibition of dentine demineralization by zinc oxide: in vitro and in situ studies. Dent Mater 2005; 21: 1170-1177.
94) Toledano M, Yamauti M, Osorio E, Osorio R. Zinc-inhibited MMP-mediated collagen degradation after different dentine demineralization procedures. Caries Res 2012; 46: 201-207.
95) Featherstone JDB. The science and practice of caries prevention. J Am Dent Assoc 2000; 131: 887-899.
96) Reynolds EC. Remineralization of enamel subsurface lesions by casein phosphopeptide-stabilized calcium phosphate solutions. J Dent Res 1997; 76: 1587-1595.
97) Gentleman E, Lotfibakhshaiesh N, Stevens MM, Hill RG, Jell G, O'Donnell MD, et al. The effects of strontium-substituted bioactive glasses on osteoblasts and osteoclasts in vitro. Biomaterials 2010; 31: 3949-3956.
98) Reginster JY, Brandi ML, Cannata-Andia J, Cooper C, Cortet B, Feron JM, et al. The position of strontium ranelate in today's management of osteoporosis. Osteoporos Int 2015; 26: 1667-1671.
99) Sasaki JI, Kiba W, Abe GL, Katata C, Hashimoto M, Kitagawa H, et al. Fabrication of strontium-releasable inorganic cement by incorporation of bioactive glass. Dent Mater 2019; 35: 780-788.
100) Takahashi Y, Okamoto M, Komichi S, Imazato S, Nakatsuka T, Sakamoto S, et al. Application of a direct pulp capping cement containing S-PRG filler. Clin Oral Investig 2019; 23: 1723-1731.
101) Okamoto M, Ali M, Komichi S, Watanabe M, Huang H, Ito Y, et al. Surface pre-reacted glass filler contributes to tertiary dentin formation through a mechanism different than that of hydraulic calcium-silicate cement. J Clin Med 2019; 8: 1440.
102) Takeda K, Kitagawa H, Tsuboi R, Kiba W, Sasaki JI, Hayashi M, et al. Effectiveness of non-biodegradable poly(2-hydroxyethyl methacrylate)-based hydrogel particles as a fibroblast growth factor-2 releasing carrier. Dent Mater 2015; 31: 1406-1414.
103) Tsuboi R, Takeshige F, Yoshimoto I, Sasaki JI, Imazato S, Kitagawa H. Development of a novel dental resin cement incorporating PGF-2-loaded polymer particles with the ability to promote tissue regeneration. Dent Mater 2018; 34: 641-648.