Review article

The Development of Remineralising and Antibacterial Dental Composites to Prevent Secondary Caries

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Abstract

The aim of this article was to provide an overview of the current development of remineralising and antibacterial dental composites to reduce bacterial microleakage leading to secondary caries which is the most common reason of composite restoration failure. The literature of up to May 2018 from PubMed and Ovid was reviewed using key words; "remineralisation", "antibacterial", and "resin composite". This review demonstrated that remineralising agents in several forms were used to enable calcium and phosphate and/or fluoride ions release from dental composites. In general, the additives successfully enhanced remineralising properties of the composites but inevitably reduced mechanical properties of the composites. The use of nanoparticles and bioactive glasses have shown to maintain composite's strength. The incorporation of antimicrobial agents into dental composites to promote antibacterial effects have also been investigated. Most of these antimicrobials contain positively charged groups which could interact with negatively charged bacterial cell membrane resulting in bacterial cell lysis. The remineralising and/or antibacterial dental composites showed promising results that could potentially help to reduce the risk of developing secondary caries. This could potentially help to increase the longevity of composite restorations.

Key words: Dental composite, Secondary caries, Remineralising agent, Antibacterial agent

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Introduction

Dental amalgam and dental composites are the commonly used materials for direct restorative treatments in high load bearing areas. Dental amalgam is a cost-effective material which exhibits good clinical longevity[1], high mechanical strength[2], and bactericidal effects[3]. It is however being phased down due to the Minamata Convention on Mercury in 2013 to reduce the potential anthropogenic emissions and releases of mercury into the environment[4]. Dental composites are then considered to be the suitable alternative material. The use of composites has also increased primarily due to the improvement of their aesthetic and physical properties in addition to the development of reliable adhesive systems[5]. The recent review in 2018 revealed that the placement of dental composites are currently attributed to 49% of all restorations[6].

Clinical studies however demonstrated the lower survival rate of dental composite restorations compared to dental amalgam restorations[7]. Mean annual failure rate of dental composite and dental amalgam restorations were 2.9% and 1.6%, respectively[8]. Furthermore, it has been shown that 74% of dental composite restorations were failed due to secondary caries. The replacement of failed restorations has been estimated to be 60% of all operative treatments[9].

Caries process is governed by several factors such as operator skills, patient related factors, and restorative materials / techniques[10]. For the material perspective, the formation of secondary caries beneath dental composites could be due to marginal leakage from improper bonding technique, polymerisation shrinkage leading to micro gap formation, tooth-composite interface degradation, and the lack of antibacterial properties[11]. Hence, several studies have focused on the improvement of dental composites to reduce susceptibilities of composites to secondary caries.

The major proposed strategies have been the incorporation of remineralising and antibacterial agents to enable the repair of demineralised dentine and reduce plaque accumulation. The aim of this review was therefore to summarise the current remineralising and antibacterial agents that have been added into dental composites.

1. Remineralisation approach

Dental caries is biofilm-mediated multifactorial/dynamic dental disease resulting in the imbalance of mineral loss (demineralisation) and mineral gain (remineralisation)[12] of enamel and dentine. Hence, restorative materials should promote mineral release to tip the mineral balance toward mineral gain thereby enhancing remineralisation and functional recovery of affected tooth structure.

1.1 Fluoride

Fluoride ion exerts anticariogenic effects such as the inhibition of bacterial enzymes and the increase in acid resistance of dental hard tissues by the formation of low soluble fluorohydroxyapatite[13]. Fluoride has been incorporated into resin composites in several forms including fluoridated glass, inorganic fluoride compounds, and pre-reacted glass ionomer filler particles (S-PRG). S-PRG fillers are produced by partial reaction between ion-leachable glass and polyalkenoic acid. Hence, the fillers allow fluoride release and recharge from the matrix. The S-PRG technology is now patented by Shofu Dental Cooperation and this reactive filler have been successfully added to dental composite which is classified as as giomer (Beuatifil™). Giomer exhibited superior flexural strength (119 MPa) and optical properties than a commercial resin modified glass ionomer cement (RMGIC) (25-77 MPa)[14]. The fluoride release of giomer was however demonstrated to be low compared to glass ionomer cements[15].

The use of fluoride nanoparticle such as CaF_2 nanoparticle promoted the release of fluoride from dental composites. The increased surface area

of small particle size could provide releasing of ions at relatively high level with low filler load. *An in vitro* study has shown that the addition of these nanoparticles enabled high fluoride release comparable to commercial RMGIC without detrimentally reduced mechanical properties of the composites[16]. Flexural strength at 24 hr of the composites containing 10 - 20 wt% of CaF_2 nanoparticles was 100 - 150 MPa which were greater than that of others commercial fluoride containing materials[17]. The strength also greater than 80 MPa required by the BS EN ISO 4049:2009 Dentistry-Polymer-based restorative materials[18]. Furthermore, an *in situ* model demonstrated that the composite containing CaF_2 nanoparticles reduced mineral loss from enamel margins which was less than half of that observed with a conventional composite[19].

Calcium phosphate compounds (CaP)

Several types of calcium phosphate compounds (CaP) that can be used in biomaterial applications are presented in Table 1. CaP have been incorporated into dental composites to enable calcium and phosphate ions release which is crucial for precipitation of biological apatites. The rate of release of these ions is governed by the solubility of CaP compounds which increases with reducing Ca/P ratio. As release also increases with decreasing pH[20], there is also the potential to provide tooth remineralisation upon acid attack. The released ions can precipitate into the more stable forms of apatite (Table1) depending upon the degree of ion saturation and pH of the environment[21]. Furthermore, it has been demonstrated that a restorative material that can promote surface apatite precipitation could potentially enable *in vitro* dentine remineralisation[22].

Table 1 Calcium phosphate compounds[23]

Name	Abbreviation	Formula	Ca/P ratio	Solubility at 25 °C (g/L)
Mono calciumphosphate monohydrate	MCPM	$Ca(H_2PO_4)2.H_2O$	0.50	~ 18
Mono calciumphosphate anhydrous	MCPA	$Ca(H_2PO_4)_2$	0.50	~ 17
Dilcalcium phosphate dihydrate (brushite)	DCPD	$CaHPO_4.2H_2O$	1.00	0.088
Dicalcium phosphate anhydrous (monetite)	DCPA	$CaHPO_4$	1.00	0.048
Octacalcium phosphate	OCP	$Ca_8(HPO_4)_2(PO_4).5H_2O$	1.33	0.0081
Calcium-deficient hydroxyapatite	CDHA	$Ca10\text{-}x(HPO_4)x(PO_4)_{6\text{-}x}(OH)_{2\text{-}x}$ (0<x<2)	1.33 - 1.67	0.0094
Amorphous calcium phosphate	ACP	$Cax(HPO_4)_y(PO_4)_z.nH_2O$ (n=3-4.5; 15-20 wt% H_2O)	1.20 - 2.20	a
a-Tricalcium phosphate	a-TCP	$a\text{-}Ca_3(PO_4)_2$	1.50	0.0025
b-Tricalcium phosphate	b-TCP	$b\text{-}Ca_3(PO_4)_2$	1.50	0.0005
Hydroxyapatite	HA	$Ca_{10}(PO_4)_6(OH)_2$	1.67	0.0003
Fluoroapatite	FA	$Ca_{10}(PO_4)_6F_2$	1.67	0.0002
Oxyapatite	OA	$Ca_{10}(PO_4)_6O$	1.67	0.087
Tetracalcium phosphate	TTCP	$Ca_4(PO_4)_2O$	2.0	0.0007

In early studies, highly soluble amorphous calcium phosphate (ACP) particles of relatively large diameter (particle diameter of up to 40 μm) were used[24]. The addition of these large particles however inevitably reduced the flexural strength of the composites to about 50 MPa. Tetracalcium phosphate (TTCP, mean particle diameter of 0.2 - 3.0 μm) from 6 to 18 wt% were added into dental composites. The composites however exhibited low flexural strength (60 - 80 MPa)[25]. A previous study has shown that dental composites containing monocalcium phosphate monohydrate (MCPM) and tricalcium phosphate (TCP) or tristrontium phosphate (TSrP) encouraged the formation of calcium-deficient hydroxyapatite upon immersion in simulated body fluid (SBF) (Figure 1)[26, 27]. Flexural strength of the composites containing 10 – 20 wt% of MCPM and TCP after ageing in SBF for 4 weeks was 118 - 139 MPa[28]. The addition of CaP also encouraged water sorption induced expansion (2 - 4 vol%) which was comparable to composite's polymerisation shrinkage (3 vol%)[29]. This was expected to help relief residual stress and gap formation at the tooth-composite interface[30].

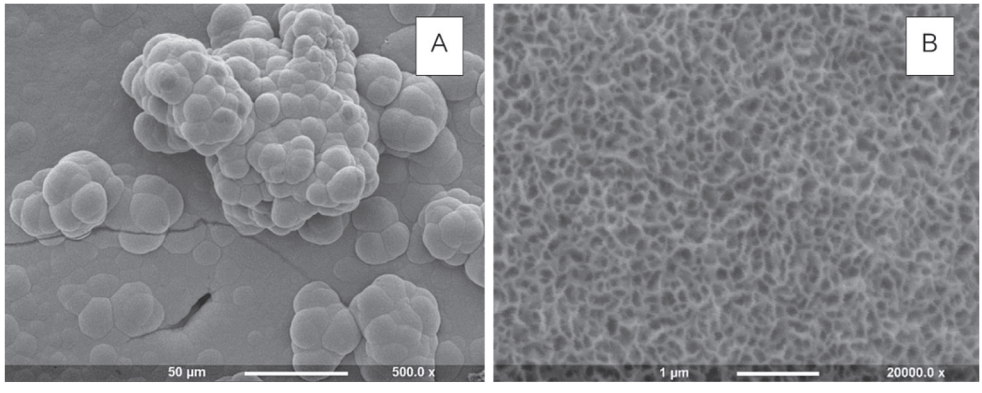

Figure 1 SEM images of calcium-deficient hydroxyapatite precipitated on surfaces of CaP containing dental composite after immersion in SBF for 4 weeks. B) A network of apatite crystals of submicron in size is clearly seen at higher magnification. From Ref (27) with permission from PLoS One.

It is known that composite strength increases with decreasing particle size[31]. Nanoparticle ACP (NACP) which the mean diameter of ~ 116 nm has been incorporated to dental composites. Composites incorporated with this nanoparticle exhibited initial strength comparable to a commercial hybrid composite in addition to the rechargeable calcium / phosphate ion release for up to 6 weeks[32]. NACP containing composites also promoted *in situ* remineralisation of adjacent enamel surface. The depth of enamel demineralisation in simulated restoration observed with NACP containing composite (14 μm) was significantly lower than that observed with conventional composites (36 μm).

1.3 Bioactive glass (BAG)

It has been reported that bioactive glasses (BAG) exhibited bone bonding ability[32]. These glasses can interact with body tissue and degrade over time thereby allowing for the controlled release of active ions[33]. The fluoride-containing BAG is therefore of interest to use in dental composites to reduce susceptibility of the composites to secondary caries. BAG can act as a single source for fluoride, calcium, strontium, and other ions depending upon its composition[34]. In general, BAG consists of oxide of silicon, calcium, phosphorus, and fluoride. It has been demonstrated that the formation of silicon-rich layer on glass's surface could act as a template for apatite precipitation[33].

The incorporation of BAG into dental composites for up to 15 wt% had no detrimentally effect on mechanical properties of the composites[35]. Mean flexural strength after 24 hr water immersion of such composites was 117 - 124 MPa. Additionally, *In vitro* study demonstrated that BAG containing composites increased the stiffness of completely demineralized dentine and also inhibited enzyme-mediated collagen degradation[36]. This may potentially help to stabilise the adhesive interface. It should be noted that BAG particles also exert antibacterial actions. The experimental composites containing 15 wt% of BAG consisting of SiO_2, CaO, and P_2O_5 reduced bacterial penetration within marginal gaps in simulated tooth restorations[37]. The average bacterial penetration depth observed with BAG containing composites was 63% of full depth whereas 100% of bacterial penetration depth was seen with conventional composite.

Strontium has been incorporated into BAG for bone repair material. It has been shown that apatite formation was increased upon replacing Ca ions with Sr ions[38]. This could be due to the fact that the strontium ions increased the potential nucleation sites for HA formation and stabilised the HA precursor phase[39]. Additionally, strontium may also provide an antibacterial effect. It also has enhanced radiopacity in comparison with calcium[40].

2. Antibacterial approach

Antibacterial actions from restorative materials are needed to help reduce bacterial microleakage at tooth-restoration interfaces. Unlike dental amalgam or glass ionomer cements, dental composites possess no antibacterial properties[11]. It has been shown that dental composites exhibited thicker biofilm formation and more plaque accumulation compared with other direct restorative materials[32]. Furthermore, the increase of cariogenic bacteria was observed on the surface of dental composites[41]. This could be due to the surface properties of the composites or the release of unreacted monomers that may affect metabolic activities of bacteria[42]. Hence, several agents have been added to dental composites to enhance antibacterial properties of dental composites.

2.1 Chlorhexidine

Chlorhexidine (CHX) has long been used in dentistry for oral infection control. It provides a wide - range of antimicrobial activity with comparable minimum inhibitory concentrations to antibiotics[20]. The release of CHX from dental composites is governed by the amount of water sorption of the composites[26]. High level of hydrophilic components in the material is therefore required to enable high CHX release. Nevertheless, the high levels of hydrophilic components might then reduce the physical and mechanical properties of the composites[43]. Furthermore, recent studies have demonstrated increasing antibiotic resistance to chlorhexidine[44]. Some severe hypersensitivity reactions resulting in death have also been reported[45].

2.2 Silver nanoparticles (AgNPs)

Silver ion is a potent antimicrobial agent but its bactericidal mechanism is not yet fully elucidated. The proposed mechanisms include cell membrane disruption, inhibition of DNA replication, and interfere with protein synthesis[46]. Silver nanoparticle (AgNPs) have been synthesised which can be combined with nanoparticle ACP to obtain composites with both antibacterial and remineralising properties[47]. Limitations of AgNPs include particle agglomeration and the discolouration of the composite[19]. Furthermore, a study has reported that bacteria can develop resistance to silver nanoparticles via genomic changes[48]. Additionally, these nanoparticles can pass the blood-brain barrier and subsequently accumulate in the brain[49].

Zinc oxide particle has been proposed to be an alternative of AgNPs. Zinc oxide particles containing composites showed better colour appearance than AgNPs and also exert antibacterial effect primarily due

to the interfering of bacterial enzymatic activities of zinc ion[50]. The efficacy of antibacterial effect of zinc ions was however much lower than that of silver ion.

2.3 Quaternary ammonium monomers (QAMs)

Polymers containing positively charged side chains such as ammonium groups have demonstrated bactericidal activities. These polymers have been incorporated in several applications including dental materials, food packaging, mouth rinse, and medical devices. The exact antibacterial mechanism of the polymers has not yet concluded but contact killing is thought to be its mechanism. QAMs cause bacterial cell lysis by the interaction between the positively charged N^+ site of monomers and negatively charged bacterial cell membrane (Figure 2)[51].

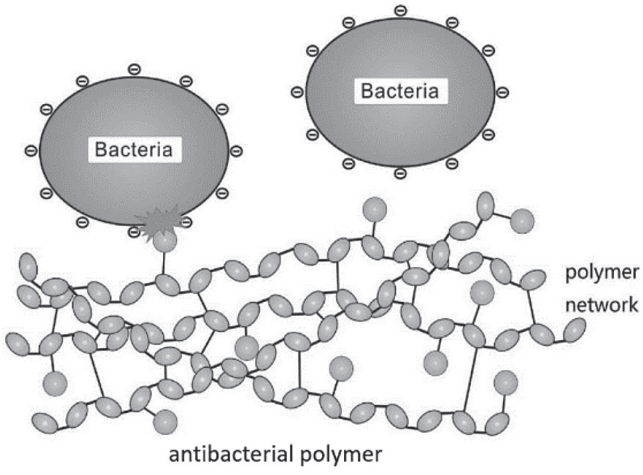

Figure 2 Illustration of the "contact killing" mechanism by the interaction between positively charged domains on quaternary ammonium monomer (QAM) and negatively charged bacterial cell membrane. Adapted from Ref (51) with permission from MDPI.

Antibacterial actions of QAM are governed by several factors such as type of compound that attaches to nitrogen, the counterion, chain length, and number of nitrogen atoms[52]. It is suggested that the addition of 5 - 10 wt% QAMs with alkyl chain length of 12 - 16 units were suitable to be used in resin composites[53]. It is also revealed that using bromide anions as the counter anion in QAMs exhibited the most potent bactericidal compared to chloride ion[54].

The polymerisable methacrylate monomer containing quaternary ammonium methacrylate (QAM) (12-methacryloyloxy dodecylpyridinium bromide; MDPB) has been successfully synthesised and used in the commercial dentine bonding agent (Clearfil SE Protect, Kuraray Medical Inc, Japan)[55]. The antibacterial component is not released after light curing. Hence, their mechanical properties were maintained[56]. Due to the immobilisation of QAMs molecule in the polymerised monomer, the resin polymer exhibited bacteriostatic effects only to the contacting bacteria[55]. Hence, it needed to combine with other antibacterial agents such as AgNAPs to enable the remote killing of bacteria[57]. The combination of these agents may further reduce mechanical properties of composites[58].

Conclusion

Dental composite is the major alternative material to dental amalgam which is now subjected to phase down due to Minamata Convention in Mercury. Secondary/recurrent caries is one of the most common reasons of failure for dental composite restoration. The addition of several remineralising agents has shown the promising remineralising effects. The addition of these compounds however reduced mechanical properties of dental composite. Using nanotechnology to produce reactive nanoparticles can help maintaining strength of the composites with the enhanced mineral ions release. Furthermore, several antimicrobial agents have been added to composites to enable antibacterial effect. Most of these compounds consist of positively charged groups that can interact with negatively charged bacterial cell membrane resulting in cell lysis. The addition of these agents could reduce susceptibility of dental composite to secondary dental caries. The promising properties of these dental composites could potentially help to increase longevity of composite restorations.

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บทคัดย่อ

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บทความนี้ได้สรุปข้อมูลจากบทความเกี่ยวกับการพัฒนาวัสดุอุดฟันชนิดเรซิน คอมโพสิต เพื่อลดการเกิดฟันผุซ้ำซึ่งเป็นสาเหตุหลักของความล้มเหลวจากการบูรณะฟันด้วยเรซิน คอมโพสิต โดยบทความวิชาการในฐานข้อมูล Pubmed และ Ovid จนถึงเดือนพฤษภาคม พ.ศ. ๒๕๖๑ ได้ถูกสืบค้นและรวบรวมโดยใช้คำสำคัญ ได้แก่ remineralisation antibacterial และ resin composite ซึ่งพบว่าปัจจุบันได้มีการนำสารประกอบหลายชนิดมาใส่ในเรซิน คอมโพสิต เพื่อส่งเสริมให้เกิดการปลดปล่อยของไอออนของแร่ธาตุต่างๆ แต่สารประกอบดังกล่าวทำให้สมบัติเชิงกลของวัสดุลดลง การนำสารประกอบระดับนาโนและแก้วไบโอแอคทีฟมาใช้พบว่าช่วยลดผลกระทบต่อความแข็งแรงของเรซิน คอมโพสิตได้ นอกจากนี้ยังมีการนำสารต้านเชื้อแบคทีเรียชนิดต่างๆ มาใช้ โดยสารดังกล่าวส่วนใหญ่จะมีองค์ประกอบที่มีประจุบวกซึ่งจะทำปฏิกิริยากับเยื่อหุ้มเซลล์ของแบคทีเรียซึ่งมีประจุเป็นลบ ส่งผลให้เกิดการรั่วซึมขององค์ประกอบในเซลล์แบคทีเรีย เรซิน คอมโพสิตที่มีองค์ประกอบของสารที่ส่งเสริมการคืนกลับแร่ธาตุและสารต้านเชื้อแบคทีเรียดังกล่าวมีสมบัติที่ช่วยลดความเสี่ยงของการเกิดฟันผุซ้ำและอาจช่วยยืดอายุการใช้งานทางคลินิกของเรซิน คอมโพสิต

คำสำคัญ: เรซิน คอมโพสิต, ฟันผุซ้ำ, สารส่งเสริมการคืนกลับแร่ธาตุ, สารยับยั้งเชื้อแบคทีเรีย