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ON THE POSSIBILITIES AND STRATEGIES FOR INCORPORATION ANTIMICROBIAL AGENTS INTO RESIN COMPOSITE DENTAL MATERIALS – A NARRATIVE REVIEW

Aleksandar Dimkov[1*]

[1]Department of Paediatric and Preventive Dentistry, Faculty of Dental Medicine, University "Ss Cyril and Methodius", Skopje, North Macedonia, e-mail: adimkov@stomfak.ukim.edu.mk

Abstract: Because of the high frequency of recurrent caries following composite resin restorative treatment, as well as the large number of cariogenic microorganisms present in the oral cavity, which represent a potential risk factor for the development of new carious lesions, the antimicrobial effects of composite resins are receiving increasing attention. Recently, attempts have been made to include specific antimicrobial compounds in restorative materials, mainly GJCs and composites, in addition to fluorides. Conventional composites' lack of antibacterial qualities implies a lack of an inhibitory impact against plaque accumulation on their surface, allowing bacteria such as mutans streptococci to grow freely. As a result, the antibacterial properties of dental resin composites are crucial to their therapeutic applications. The present study demonstrates the methods and possibilities for incorporating antimicrobial chemicals, both leachable and non-leachable, into the resin matrix or filler of composite resins.

Keywords: *Dental Resin Composite, Antibacterial Agents, Antibacterial Strategies, Caries prevention.*
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1. INTRODUCTION

Resin composite dental materials and adhesives together with glass-ionomer cements are today's modern restorative dentistry. Both materials have exceptional qualities; but, because of their bioactivity and superior biocompatibility with dental tissues, GICs are preferred, particularly for primary tooth restorations. Despite their near-perfect development, composites nonetheless have some flaws. In addition to disadvantages such as ensuring an ideal dry working field (which necessitates the use of a rubber dam), the cost of the restoration, the therapist's possession of certain skills, and durability, perhaps the most significant disadvantage is composite shrinkage followed by microleakage and the occurrence of secondary caries around the restorations. Regardless of the fact that the latest generations of composite resins and dentin adhesives reduce the occurrence of these phenomena, as much as 60% of re-restorations account for the occurrence of secondary caries at the margins around the composite restoration, which costs the United States alone approximately $5 billion per year. Although secondary caries is initially imperceptible to the human eye, the ongoing carious activity induced by bacteria causes the surrounding dentin and enamel to deteriorate, as well as the prior restorative. When this occurs, the changes become visible, and the patients begin to feel changes, which are usually painful sensations to certain stimuli, and the subsequent procedure necessitates the removal of the restoration as well as a portion of the hard dental tissues affected by caries, followed by the application of a new composite restoration. This can frequently result in a "circulus vitiosus" that never ends. This is the fundamental issue that necessitates the development of solutions and strategies. The first solution would be minimal intervention dentistry, also known as minimally invasive dentistry, in which just the affected section of the hard tooth structure is removed without unwanted cavity expansion. Dental adhesives have played a vital part in the revolution of restorative and preventative dentistry, as well as in paving the path for minimally invasive dentistry. Clinicians can utilize adhesives to create a more conservative cavity design, protecting healthy tissue because mechanical retention is no longer necessary. The second solution would be to create new tools to identify, monitor, and stop these lesions in their early stages by stopping them and bracing remineralization. The creation of restorative materials with long-term antibacterial capabilities is the third solution. Sustained antimicrobial action would allow for the continued decrease of demineralization, preventing the course of the defect and supporting remineralization.

*Corresponding author: adimkov@stomfak.ukim.edu.mk

2. DENTAL COMPOSITE RESIN MATERIALS

The application of composite restoration requires the use of two equally important materials – adhesive and composite resin, but the focus in this review will be primarily on composite resins which are commonly used in contemporary dentistry. Dental composite restorative materials or dental composite resins are also known as "resin-based composites". They are dental cements that contain synthetic resins and inorganic filler. Bis-GMA and other dimethacrylate monomers are frequently utilized in composite resins. A filler material usually is silica, and in most composites, has built-in a photoinitiator and other catalyst systems. In a resin matrix, strong inorganic particles are bonded together. Bis-GMA, hydroxyethyl methacrylate (HEMA), triethylene glycol dimethacrylate (TEGDMA), and urethane dimethacrylate (UDMA) are the most common resin-based oligomer matrix components. Silicon dioxide (silica), quartz, silica glass including barium, strontium, zirconium, and ceramic fillers are examples of inorganic fillers commonly used in composites. These fillers can increase the hardness, wear resistance, and transparency. of the composite. Organic silanes, such as 3-methacryloxypropyltrimethoxysilane (3-MPS) and 10-methacryloyloxydecyl dihydrogen phosphate (10-MDP), are widely utilized in coupling agent systems because their chemical functional groups can boost bonding strength between the reinforcing filler and the resin matrix. When external energy is applied, several types of photoinitiators are used to initiate composite polymerization: trimethyl benzoyldiphenylphosphine oxide (TPO), benzoyl peroxide (BPO), camphorquinone (CQ), phenanthrenequinone (PQ), benzophenone (BP), and 1-phenyl-1,2 propanedione (PPD). To regulate the rate of polymerization, a catalyst is applied. Other ingredients, such as dimethylglyoxime (dmgH2), colorants such as metallic oxide, stabilizer systems, and curing-promoting agents such as catalysts, can also be employed to improve physical attributes such as flowability.

Several categorization methods have identified a wide range of composite products for clinical usage. The most essential classification of dental composites is most likely into four major types. According to this categorization, they can be divided into four categories and several subcategories 1. according to restorative procedures (direct and indirect); 2. according to filler particle size (macro filled, micro filled, hybrid, nanocomposites); 3. according to clinical applications (packable, flowable, polyacid modified, self-adhesive, osmotic, bulk-fill) and 4. according to curing modes (chemically activated, light-activated, heat-cured, dual-cured).

This brief narrative review aims to summarize existing information regarding the potential benefits of adding antimicrobial chemicals into resin composite materials, kinds of agents, methods of application, and modalities using data from the literature.

3. STRATEGIES FOR THE DEVELOPMENT OF ANTIMICROBIAL COMPOSITES

Oral biofilms cannot be prevented by dental restorations, notably composites, and it has even been observed that biofilms are more prone to grow on the surface of restorations. As a result, efforts have been made to produce innovative resin composites capable of suppressing oral biofilms. Antibacterial properties of restorative materials are required to aid in the reduction of bacterial microleakage at tooth-restoration interfaces. Dental composites, unlike dental amalgam or glass ionomer cements, do not have antimicrobial qualities. Dental composites have been proven to generate thicker biofilms and accumulate more plaque than other direct restorative materials. Furthermore, cariogenic bacteria were shown to be more prevalent on the surface of dental composites. This might be related to the surface features of the composites or the release of unreacted monomers, which could alter bacterial metabolic activity. As a result, including antimicrobial properties into dental resin composites is of great interest for both research and therapeutic applications.

Numerous investigators have developed novel antibacterial and bioactive therapeutic dental composites. In the 1950s, Colton and Ehrlich (1953) applied antibiotic medications in resins for direct filling to provide resins with bactericidal qualities. Since that time, extensive research has been conducted on the many methods and possibilities for integrating antimicrobial components into composite resins. According to the literature, antimicrobial composites may be developed by including antimicrobial agents that release or do not release into the resin matrix or in the inorganic filler. As a result, there are several strategies for developing antimicrobial dental resin composites, depending on the type of antimicrobials and the constituent part of the composite where antimicrobials are incorporated, which are referred to differently by different authors but are essentially the same thing. Xue, et al. (2020) divided antimicrobials into filler-type and resin-type. Chen, L., Suh BI., Yang J. (2018) divided antimicrobials into leachable antibacterial agents, polymerizable antibacterial agents, and filler particles. Sun, Q., et al. (2012) classified composite resin antimicrobial methods into three types: antimicrobial agent release techniques, contact-dependent strategies, and multi-functional strategies. According to them, another strategy is the development of so-called antifouling dental resins with the goal of deterring microbial adherence and

modifying the composition of biofilms. Alansy, AS., et al. (2022), categorize antimicrobial approaches based on antibacterial agents in leachable agents; polymerizable monomers which are subdivided into polymerizable monomers used alone and polymerizable monomers in combination with leachable agents, and antibacterial filler particles divided into metal filler, metal oxide filler, and bioactive filler. Pinto (2019) classified antimicrobial agents into releasing and non-releasing agents. According to Ren, J., & Guo, X. (2023), contact killing and filler-release killing of germs are two concepts for the creation of antimicrobial dental composites.

The filler-type method is typically connected with antimicrobial component burst release, leading to in an immediate decrease in antibacterial activity. From now on, the resin-type approach has the advantage of restricting the antimicrobial components released via covalent bonding, retaining long-term antibacterial properties.

An antimicrobial agent may be dissolved in the resin monomers of the composite or combined with filler particles to form an antimicrobial resin composite if the antimicrobial agent is not soluble in the resin monomers (Chen et al., 2018). According to Featherstone (2022), only 4 agents incorporated in composite resins are commercial products, particularly, benzalkonium chloride, chlorhexidine, glutaraldehyde, and 12-methacryloyloxydodecylpyridinium bromide.

4. LEACHABLE OR RELEASING ANTIBACTERIAL AGENTS

Many leachable antimicrobial ingredients have been used in dental composites, including antibiotics, fluoride, chlorhexidine (CHX), alexidine, chitosan, carolacton, octenidine dihydrochloride, etc. The impact of releasing agents is linked to the release of antibacterial compounds at a distance, and they may affect the physical qualities of the material. Because leachable compounds are often water-soluble, Under oral conditions, they might be released into the restorative region. Benzalkonium chloride (BKC) and CHX are the most often utilized leachable antibacterial agents in dental materials. BKC is a quaternary ammonium compound (QAC) that is positively charged. One downside of leachable compounds is their quick initial release of antibacterial agents (burst effect), which is followed by a rapid reduction in antimicrobial activity. As a cationic surfactant, CHX disturbs microorganisms by linking positively charged amino groups to negatively charged bacterial cell walls. Because of its increased solubility at lower pH values, it is released faster in lower pH conditions.

Triclosan (TCN) is a leachable antibacterial agent that is often used in resin-based composites. Similarly, because of the short-term burst impact, TCN is typically integrated into specific “vehicles” known as nanotubes. TCN was effectively encapsulated into halloysite nanotubes (HNT/TCN), which were used to make the micro-hybrid dental resin composite at 8% w/w. (Zhu et al., 2012). Instead of CHX and TCN, octenidine dihydrochloride and carolacton were discovered to be more efficient antibacterial agents for significantly reducing biofilm development and more effective antibacterial activity (Apel et al., 2013). Aside from changing the monomers of the resin, another method of contact killing involves adding antimicrobial peptides (AMPs) to the resin. AMPs are naturally occurring small molecule peptides that can kill bacteria without causing resistance. Natural AMPs have been shown to be effective against cariogenic bacteria like Streptococcus mutans. Because the majority of AMPs have positive charges, they are known as cationic antimicrobial peptides. (Zhang et al., 2016).

5. NON-LEACHABLE OR POLYMERIZABLE ANTIBACTERIAL AGENTS

Antimicrobial polymers in dental resin begin as antimicrobial monomers since dental resin composite is unpolymerized and is either self-cured or light-cured following polymerization. Although QACs, chitosan, and imidazole have all been described as possibly leachable compounds, they can covalently copolymerize with the resin matrix, remaining immobilized and released over time. As a result, they act by coming into close touch with microorganisms providing long-term antibacterial protection. A common polymerizable antimicrobial agent consists of a polymerizable group (which is usually (meth)acrylate), an antibacterial functional group (which is typically cationic groups like quaternary ammonium, pyridinium, or phosphonium), and an alkyl chain spacer. Antibacterial monomers are not predicted to leach out of resin composites after copolymerization, likely resulting in long-lasting antibacterial benefits via the prevention of bacterial growth on the composite surface upon contact. One downside of immobilizing polymerizable chemical substances is that they can only kill germs upon contact, so according to Ren & Guo (2023), the compounds from this group are called contact-killing agents.

QACs are the most often used antibacterial agents in this technique. As previously noted, QAC antibacterial agents generally existed in the form of small molecular compounds, and their effects were typically unstable. To address this issue, scientists created a large number of stable macromolecular QAC monomers by copolymerizing QAC groups with organic monomers. Methacryloyloxy-dodecyl pyridinium

bromide (MDPB) was the first and one of the most essential QAC monomers for creating antimicrobial dental resin composites in 1994. MDPB was given antibacterial and polymerizable characteristics by the addition of a methacryloyl group. It may successfully copolymerize with common methacrylates when made into a dental filling composite constituted of Bis-GMA, TEGDMA, and DMAEMA at weight percentages of 0.1% and 0.2%, respectively.

QACs may be introduced to dental composites in two ways: as a polymerized QA monomer or as a QA component of a filler. Liang, X., et al. (2014) investigated a series of QA dimethacrylate monomers in bisphenol A-glycidyl methacrylate/trimethylene glycol dimethacrylate dental resin systems for antibacterial activity, as did Chrószcz, MW., et al. (2022) who reported work on copolymers based on QA urethane-dimethacrylate analogs and triethylene glycol dimethacrylate. They demonstrated in laboratory models that the copolymers they created have remarkable physical qualities as dental materials as well as significant antibacterial capabilities.

2-Methacryloyloxyethyl Phosphorylcholine (MPC) was created by first preparing PCs (phosphorylcholine analogs) that would act on the outer bilipid membrane of bacterial cells that contained zwitterionic lipid phosphatidylcholine. Incorporating MPC and a quaternary ammonium dimethylaminohexadecyl methacrylate (DMAHDM) into dental composite improved suppression of biofilm formation and lactic acid generation. It was proposed that DMAHDM had a significant part in the antimicrobial activity, whereas MPC aided this process by acting as a protein repellent, resulting in a synergistic effect. DMAHDM, incorporated into experimental dental composites demonstrated good biofilm inhibition (Clarin et al., 2021).

Deep eutectic solvent (DES) is a physically manufactured eutectic combination with ionic liquid-like physiochemical characteristics. Wang, et al. (2020) synthesized an antibacterial drug, benzalkonium chloride, and obtained polymerizable DES, paving the way for DES to have dual roles of bacteria suppression and polymerization. Hwang, et al. (2017), found that combining a polymerizable antibacterial imidazolium-containing resin (ABR) with a methacrylate-based modified composite (ABR-MC) changed biofilm architecture by limiting Streptococcus mutants' capacity to form structured bacterial clusters.

Bhadila, et al. (2021) created a resin that comprises urethane dimethacrylate, triethylene glycol divinyl benzyl ether, 3% dimethylamino hexadecyl methacrylate, and 20% amorphous calcium phosphate nanoparticles. The resin contains both antimicrobial and remineralizing components, and the experimental model indicated that antibacterial properties could be maintained for several months in an acidic environment with a biofilm. Antimicrobial compound alterations of triclosan and chitosan as linked to a methacrylate monomer and added to the composite resin have been studied in recent years. (Stenhagen et al., 2019).

6. INCORPORATING ANTIBACTERIAL FILLER PARTICLES

Another method for creating an antimicrobial resin composite is to include antibacterial particles in the fillers or resin matrix, which can release small ions to provide antibacterial effects. Polymeric nanoparticles such as (QPEI), bioactive glass (BAG), metals, metal oxides, or metal salts are normally insoluble but can release small quantities of ions, resulting in antimicrobial action. QA compounds used as fillers in dental materials can be made from materials that have been mixed with a filler such as silica or with a polymer such as QA polyethylenimine (QPEI). When the powerful antibacterial QA is polymerized to form minute particles, QPEI is produced. The incorporation of cross-linked QPEI into dental resin composites induced antibacterial activity throughout time (at least one month) without affecting mechanical properties (Shvero et al., 2015). The first generation of QA insoluble antibacterial particles, QPEI, was developed to kill microorganisms on direct contact. A second generation of particles that combine QA with inorganic silica as the core and expose the same functional groups as QA has recently been produced. These new particles, dubbed QASi, have the same antibacterial properties as QPEI and do not deteriorate with time. The integration of QASi into dental materials has been found to improve compatibility with the composition of resin-based dental materials, hence lowering its effect on mechanical and esthetic aspects important in restorative dentistry (Rechmann et al., 2012).

Because of its alkalinity, bioactive glass (BAG) is known to have antibacterial properties, and the incorporation of alkali-ion substituted calcium phosphate fillers into experimental dental composites resulted in a decrease in the bacterial population with no adverse effects on the composite's physical properties (Khvostenko et al., 2016). The incorporation of nano-silver particles into composite resin inhibited bacterial growth considerably. The addition of zinc oxide to the composite greatly decreased bacterial growth while having no negative impact on physical strength.

Several nanoparticles, including Ag, Cu, ZnO, and chitosan, have been introduced into composite resin as release additives to regulate biofilms. In recent decades, silver nanoparticles (AgNPs) have

developed as a research hotspot. While the antibacterial mechanism of AgNPs is unclear, it is widely assumed that silver nanoparticles have a bactericidal impact via their intrinsic bactericidal activity as well as the release of Ag+. Most prior studies concluded that adding AgNPs to restorative materials had little effect on their mechanical qualities; nonetheless, AgNPs may interfere with the dental resin polymerization process. Unlike Ag, ZnO nanoparticles are harmless and have a hue comparable to real teeth, therefore they have gained significant attention (Yin et al., 2020; Wanget al., 2020). Another type of metal oxide, titanium dioxide nanoparticles (TiO2 NPs), is frequently employed to alter resin composites as an antibacterial agent. These composites greatly decreased biofilm development with no variations in their composition (Dias et al., 2019). Additionally, for enhanced performance, the nanoparticles may be coated with chemicals such as phenols and antibiotics (Wang et al., 2017).

Chewing and abrasion gradually release typical releasable antibacterial chemicals added to the resin. Their release rate, on the other hand, fluctuates, resulting in a significant initial release within a few months following cavity filling and a modest long-term release influence. As a result, a carrier capable of slowing and constant antibacterial medicine release is necessary. New antimicrobial compound release technologies have been advocated in recent years in order to retain the mechanical qualities of composite resins while also reducing the release rate of antimicrobial compounds. Mesoporous silica nanoparticles (MSNs) are potential drug carriers because they can store significant quantities of pharmaceuticals in their pores and prolong release by inhibiting drug diffusion (Yamamoto & Kuroda, 2016). In that regard, the synthesis of Zn-doped mesoporous silica nanoparticles or coated ZnO particles with mesoporous SiO2 to produce ZnO@m-SiO2 is also discussed. Similarly, Stewart et al. (2018) created an antimicrobial-drug-silica co-assembled particle system using octenidine dihydrochloride to construct a heavily loaded (35% wt.) particle. OCT-silica nanocomposite CHX was encapsulated using mesoporous silica nanoparticles to enhance its long-term release, and composites containing encapsulated chlorhexidine demonstrated regulated chlorhexidine release over a long length of time (Bai et al., 2020; Chen et al., 2018). Furthermore, a composite material with significant antibacterial activity was created by mixing montmorillonite (MMT), a nano clay used as a pharmaceutical ingredient for controlled drug release, with CHX (Boaro et al., 2019). Scientists have investigated novel kinds of agents to limit bacteria adhesion and biofilm formation in addition to conventionally released antimicrobial agents, such as silver sodium hydrogen zirconium phosphate (SSHZP), a silver-releasing ceramic incorporated into light-curing resin composites, and essential oils, which contain volatile aromatic components with antibacterial activity against caries-related microorganisms. (Stencel et al., 2018).

7. MULTI-FUNCTIONAL STRATEGIES

There are two types of multi-functional strategies: those that combine two or more antimicrobial additives, and those that combine leachable/non-leachable agents with remineralization. The combination of antibiofilm agents and remineralization procedures is on the research horizon. In the literature, the following combinations can be found: MPC+DMAHDM, NACP+QADM+Nag, NACP+DMAHDM, NACP+DMAHDM+MPC, exhibiting synergistic antibacterial activity (Bhadila et al., 2020; Balhaddad et al., 2020).

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