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Incorporation of antibacterial agent derived deep eutectic solvent into an active dental composite

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ABSTRACT

Objective. To incorporate an antibacterial agent derived deep eutectic solvent (DES) into a dental resin composite, and investigate the resulting mechanical properties and antibacterial effects.

Method. The DES was derived from benzalkonium chloride (BC) and acrylic acid (AA) and was incorporated into the dental resin composite through rapid mixing. A three-point bending test was employed to measure the flexural strength of the composite. An agar diffusion test was used to investigate antibacterial activity. Artificial (accelerated) aging was undertaken by immersing the composites in buffer solutions at an elevated temperature for up to 4 weeks. UV–vis spectrophotometry and NMR analysis were conducted to study BC release from the composite. Finally, the biocompatibility of the composite materials was evaluated using osteoblast cell culture for 7 days. Results were compared to those of a control composite which contained no BC.

Result. The DES-incorporated composite (DES-C) displayed higher flexural strength than a similar BC-incorporated composite BC (BC-C) for the same level of BC. The inclusion of BC conferred antibacterial activity to both BC-containing composites, although BC-C produced larger inhibition halos than DES-C at the same loading of BC. Control composites which contained no BC showed negligible antibacterial activity. After artificial aging, the DES-C composite showed better maintenance of the mechanical properties of the control compared with BC-C, although a decrease was observed during the three-point bending test, particularly upon storage at elevated temperatures. No BC release was detected in the aged solutions of DES-C, whereas the BC-C showed a linear increase in BC release with storage time. Significantly, cell viability results indicated that DES-C has better biocompatibility than BC-C.

Significance. The incorporation of a BC-based DES into a dental resin composite provides a new strategy to develop antibacterial dental materials with better biocompatibility and

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longer effective lifetimes without sacrificing the intrinsic mechanical properties of the composite structure.

1. Introduction

Dental resin composites are the most commonly used materials for dental restorations due to their aesthetic properties, mechanical strength, safety, and reasonable cost [1]. However, in comparison with amalgam restorations, the most significant disadvantage of using a resin composite is a higher risk of secondary caries [2]. If secondary caries occur, the resin composite requires removal and replacement, which results in additional tissue loss. Bacteria around the resin composite are considered the primary cause for the occurrence of secondary caries [3]. Notably, dental biofilms have been found to accumulate more on a resin composite than on enamel or other restoration surfaces [4]. Moreover, the inherent polymerization shrinkage of composites can cause micro-leakage between the prepared tooth and restorative materials [5]. Bacterial mobilization between micro-leakages increases the subsequent risk of dental decay. Therefore, a dental resin composite coupling excellent mechanical performance with long-lasting antibacterial activity is in high demand.

Because dental resin composites are principally composed of fillers and resin matrix, previous efforts to achieve antibacterial composites have mainly focused on modification of either the filler components or the resin matrix [6]. For example, Aydin Sevinç and Hanley [7] blended 10 wt% zinc oxide (ZnO) nanoparticles into dental composites as filler, and an 80% reduction in bacterial counts were observed compared to a control group. However, Hojati et al. [8] reported that the antibacterial properties declined significantly during aging tests. Silver-modified fillers can also provide antibacterial properties [9,10], but they need to be loaded at about 10–20 wt% to give comparable antibacterial performance. Unfortunately, high loading of the dental filler with antibacterial materials negatively impacts the desired mechanical properties of the composite [11]; therefore, addition of an antibacterial agent to the dental resin should be considered. Jedrychowski et al. [12] and Takemura et al. [13] added chlorhexidine into a dental resin composite, and more recently Othman et al. [14] employed benzalkonium chloride. However, it has been reported that directly incorporating antibacterial agents into dental resins can similarly reduce the mechanical strength of the composites [15]. Rapid release of the antibacterial agent is considered as another drawback of this strategy: a chlorhexidine-loaded composite has been reported to release up to 50% of the initial loading within 14 days [16]. Moreover, the leaching-out of the antibacterial agent may produce porous structures within the composite, increasing the risk for polymer degradation and failure of restorations [17]. In another example, Imazato et al. [18] introduced an antibacterial monomer 12-methacryloyloxydodecylpyridinium bromide (MDPB)—which couples an antibacterial agent and a polymerizable methacryloyl group—for covalent incorporation into a resin composite. From their experimental results, antibacterial properties were observed without a significant influence on the mechanical properties and a non-releasing antibacterial composite was successfully obtained. Despite favorable performance, the requirement for synthesis of the MDPB monomer will likely limit the adoption of this approach relative to those that solely employ commercially-available reagents.

Recently, deep eutectic solvents (DESs) formed by mixtures of choline chloride and urea were reported by Abbott et al. [19] and have since attracted extensive research interest. Abbott et al. [20] further defined four types of DES of which Type III DESs, formed from a quaternary ammonium salt with a halide anion and a hydrogen bond donor, appear most attractive for exploration in dental composites [21]. Compared to traditional ionic liquids (ILs), DESs share the properties of high viscosity, low vapor pressure, and good thermal stability, while having the advantages of convenient synthesis (typically, by reaction-free mixing) at lower costs and often with improved biodegradability and lower toxicity [22]. DESs have been successfully applied in the areas of polymer science [23], nanomaterials synthesis [24], electrochemistry [21], and drug delivery [25]. Benzalkonium chloride (BC) is a commonly used active ingredient for clinical, food line, and domestic household biocides [26,27]. In the dental area, BC has been incorporated into dental etchants for antibacterial purposes [28]. Because it comprises a quaternary ammonium cation paired with a halide, we reasoned that BC could be converted to a Type III DES by mixing with a suitable hydrogen bond donor species. Carboxylic acids represent some of the most commonly used hydrogen bond donors in DES formulation [29]. In our work, acrylic acid (AA) was selected as the hydrogen bond donor. The simplest unsaturated carboxylic acid possible, not only is AA produced on the million-ton scale annually, but it consists of a vinyl group connected directly to a carboxylic acid terminus, allowing for polymerization with the aid of a radical initiator or a catalyst.

In the present study, a DES comprising BC and AA was incorporated into a dental resin composite to develop an antibacterial dental composite. The vinyl group in AA allows incorporation of the DES within the polymerized composite matrix through covalent bonding, while the antibacterial agent of BC remains hydrogen bonded to the matrix and is responsible for imparting antibacterial activity. This novel strategy proved to be easy and convenient to perform. The antibacterial activity, antibacterial agent release, flexural strength, and biocompatibility of the DES-incorporated composites (DES-C) were evaluated and compared to the prop-

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