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Photocurable bioactive bone cement based on hydroxyethyl methacrylate-poly(acrylic/maleic) acid resin and mesoporous sol gel-derived bioactive glass

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ABSTRACT

This paper reports on strong and bioactive bone cement based on ternary bioactive SiO_2-CaO-P_2O_5 glass particles and a photocurable resin comprising hydroxyethyl methacrylate (HEMA) and poly(acrylic/maleic) acid. The as-cured composite represented a compressive strength of about 95 MPa but it weakened during soaking in simulated body fluid, SBF, qua its compressive strength reached to about 20 MPa after immersing for 30 days. Biodegradability of the composite was confirmed by reducing its initial weight (~32%) as well as decreasing the molecular weight of early cured resin during the soaking procedure. The composite exhibited *in vitro* calcium phosphate precipitation in the form of nanosized carbonated hydroxyapatite, which indicates its bone bonding ability. Proliferation of calvarium-derived newborn rat osteoblasts seeded on top of the composite was observed during incubation at 37 °C, meanwhile, an adequate cell supporting ability was found. Consequently, it seems that the produced composite is an appropriate alternative for bone defect injuries, because of its good cell responses, high compressive strength and ongoing biodegradability, though more *in vivo* experiments are essential to confirm this assumption.

1. Introduction

Acrylic cements have been extensively used in orthopedic surgery for fixation of devices such as total hip implant stems or knee joint prosthesis. These cements are self-curing systems and composed of two parts: Powder phase, which is mainly polymethyl methacrylate (PMMA) and barium sulfate radiopacifier and liquid phase that is methyl methacrylate (MMA) monomer. A setting reaction happens when the powder and liquid phases are mixed to each other [1]. The main advantage of acrylic cements is high mechanical strength which makes them appropriate for load-bearing applications. However, the following drawbacks can be pointed out for acrylic cements: Volume contraction due to the polymerization phenomenon, which would result in aseptic loosening, the exothermic setting reaction that leads to necrosis of surrounding tissue and lacks of osteoconductivity and bioactivity [1–3] that fails the cement bone bonding ability. Moreover, traditional acrylic bone cements are chemically stable in the body, *i.e.* they are not degraded and thus, no bone replacement occurs.

Recently, some efforts have been made to improve some drawbacks of PMMA bone cements. Table 1 summarizes the chemical composition and compressive strength of the recently developed resin-based bone cement with improved bioactivity. The cement formulations have been developed in three categories: The first group, cements in which a bioactive filler is combined with the traditional cement powder (PMMA) and the resin phase is MMA monomer [4–13]. These include addition of hydroxyapatite, bioactive glass, calcium phosphates and glass-ceramic particles to the common PMMA cement formulation. In second activities, one or more bioactive agent is mixed with the cement powder or directly added to the resin phase other than MMA only [14–26]. In another group, bioactivity is achieved without using a bioactive filler, *e.g.* by providing functional groups on cement surfaces, which are capable for apatite formation and bone bonding [27,28]. In the first group, the disadvantages of PMMA cements still remain. As observed in Table 1, for the second group, the resin phase of some modified bioactive bone cements is Bis-GMA. Although bioactive bone cements based on Bis-GMA give adequate mechanical properties, unfortunately, it has been reported that Bis-GMA is oestrogenic and may be released into the surrounding environment [29,30].

Calcium phosphate cements (CPCs) are other alternatives for bone treatments. CPCs are self-setting inorganic materials, which consist of a powder phase comprising a mixture of acidic and basic calcium phosphate salts (*e.g.* tetracalcium phosphate and dicalcium phosphate) and a liquid phase, which is usually an aqueous solution of phosphate salts along with some cohesion promoters [31]. CPCs are biocompatible and bioactive materials which are osteoconductive and even osteoinductive (when incorporating with some biological factors). They can be also injected into the defects in minimal invasive surgeries [32]. However,

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Table 1
Formulation and characteristics of some resin-based bioactive bone cements.

Resin phase	Solid polymeric phase	Bioactive filler phase	Setting mechanism	Compressive strength (MPa)	Reference
MMA	PMMA + $BaSO_4$	HA, Sr-HA, Bioactive glass beads (MgO-CaO-SiO_2-P_2O_5-CaF_2), A and AW glass-ceramics, HA + chitosan, Recombinant human growth hormone, particles of cancellus bone, β-TCP, α-TCP, NaF_2,	Self-curing	70–130 depending on the filler type, size and content	[4–13]
MMA + DEAEMA	PMMA	HA, α-TCP	Self-curing	–	[14]
Bis–GMA + TEGDMA	–	Sr-HA, Bioactive glass beads (CaO-SiO_2-P_2O_5-CaF_2), β-TCP, HA and AW glass- ceramic (MgO-CaO-SiO_2-P_2O_5-CaF_2), Fumed silica, fused silica, apatite-wollastonite glass-ceramic	Self-curing	100–195 depending on the filler type, size and content	[15–19]
Bis–GMA + TEGDMA + MMA	–	Epoxy–SiO_2 hybrid sol–gel material	Self-curing	126	[20]
UDMA + TEGDMA	–	HA	Self-curing	184	[21]
4-META + MMA	PMMA	HA	Self-curing	20–50 depending on HA content	[22]
*n*BMA	PEMA	HA, silanated HA, silicate HA	Self-curing	–	[23]
MMA + EGDMA		Silica-PMMA	Light-curing	–	[24]
Bis–GMA + TEGDMA		Barium silicate glass + E-glass fiber	Light-curing	850–900 (bending strength)	[25]
HEMA + PAMA		TTCP + DCPA	Light-curing	50–80 depending on the filler content	[26]

Abbreviations: PMMA,: polymethylmethacrylate, PEMA: poly(ethyl methacrylate), BMA: butyl methacrylate, META: methacryloyloxyethyl trimellitate anhydride, MMA: methyl methacrylate, DEAEMA: diethyl amino ethyl methacrylate, UDMA: urethane dimethacrylate, TEGDMA: triethyleneglycol dimethacrylate, HEMA: hydroxyethyl methacrylate, PAMA: poly(acrylic-maleic) acid, HA: hydroxyapatite, Sr-HA: strontium-containing hydroxyapatite, A: apatite, AW: apatite-wollastonite, TTCP:tetracalcium phosphate, DCPA: dicalcium phosphate,α-TCP: alpha-tricalcium phosphate, β-TCP: beta-tricalcium phosphate.

CPCs have a very slow resorption rate, meanwhile they are mechanically weak as their applications are just advised for non-load-bearing sites such as craniofacial and maxillofacial reconstruction [33,34].

For the self-setting biomaterials (*e.g.*, CPCs and resin based bone cements), setting time is a very important issue that should be considered by manufacturers. The setting time is greatly influenced by different factors, such as cement composition, particle size, temperature and powder to liquid mixing ratio. In orthopedic surgeries, the hardening reaction of self-setting materials may be problematic. The long setting time prolongs the surgical time, while the fast hardening process decreases the accuracy of operation as well as the efficiency of manipulation, resulting in an improper treatment. As shown in Table 1, the bioactive bone cements are commonly self-setting materials, though some photocurable composites have been also developed.

Designing a biodegradable and strong bioactive bone cement (comparable to PMMA cement), with manageable setting behavior and minimal immunologic reactions can be ideal for bone defect treatment. Accordingly, in this study, a novel bioactive bone cement based on mesoporous sol-gel derived bioactive glass particles and photocurable poly(hydroyethyl methacrylate)/poly(acrylic-maleic) acid resin has been developed. The mechanical strength, apatite formation ability, *in vitro* biodegradation and cell behavior of the introduced cement were also evaluated.

2. Materials and methods

2.1. Starting materials

Bioactive glass was selected based on $64SiO_2$-$31CaO$-$5P_2O_5$ ternary system and synthesized trough a sol-gel method according to the previously described process [35]. All reagents used for the synthesis of bioactive glass were purchased from the Merck Company. The bioactive glass powder was ground in an agate mortar to reach an average particle size of 1 μm. A commercially available resin, Fuji (Fuji II LC, Japan), comprising hydroxyethyl methacrylate (HEMA), poly(acrylic/maleic) acid (PAMA) and camphorquinone photoinitiator, was also employed as the polymeric component of the composite.

2.2. Composite preparation

The composite was prepared by mixing the bioactive glass powder and Fuji resin, followed by light curing in a glassy tube-shaped holder. Hence, in a cured cylindrical specimen, each of the surfaces had been irradiated 80 s, according to the resin manufacturer's notification. In order to have an optimum powder to resin ratio, various pastes with different solid (bioactive glass) to liquid (resin) proportions (0.5, 0.8, 1.1 and 1.2 g/ml) were made and tested in terms of consistency [26]. In brief, the powder and the liquid phases were thoroughly homogenized and the uncured paste was pressed between two glassy slabs at a constant compressive load of 20 N. The maximum solid to liquid ratio, in which a paste without edge-cracking was obtained, was considered for composite preparation and further experiments.

2.3. Experimental

2.3.1. Bioactive glass characterization

The particle size distribution of the bioactive glass powder was measured in ethanol medium using a laser particle size analyzer (Fritsch analysette 22). To observe the morphology of the synthesized bioactive glass, a transmission electron microscopy with an accelerating voltage of 200 kV was employed (TEM, GM200 PEG Philips). The glass powder was dispersed in ethanol under ultrasonic condition until a diluted suspension was formed. A droplet of the suspension was dropped on carbon-coated copper grids for the TEM analysis.

The nitrogen adsorption–desorption isotherms were recorded at 77 K using a Quantachrome Autosorb 1 sorption analyzer. All the samples were degassed for 12 h at 150 °C under high vacuum condition. The pore size distribution of the powder was determined by the volume of adsorbed N_2. The specific surface area (SSA) of the powder was also determined using Brunauer-Emmett and Teller method (BET, ASAP 2010, Micromeritics, USA), based on the volume of the adsorbed nitrogen against the relative pressure.

2.3.2. Acellular in vitro studies

In this part of the study, at first, simulated body fluid (SBF) solution was prepared according to the Kokubo's specification [36] using pure