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Aluminum-free glass-ionomer bone cements with enhanced bioactivity and biodegradability

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ABSTRACT

Al-free glasses of general composition $0.340SiO_2:0.300ZnO:(0.250\text{-}a\text{-}b)CaO:aSrO:bMgO:0.050Na_2O:0.060P_2O_5$ (a, $b = 0.000$ or 0.125) were synthesized by melt quenching and their ability to form glass-ionomer cements was evaluated using poly(acrylic acid) and water. We evaluated the influence of the poly(acrylic acid) molecular weight and glass particle size in the cement mechanical performance. Higher compressive strength (25 ± 5 MPa) and higher compressive elastic modulus (492 ± 17 MPa) were achieved with a poly(acrylic acid) of 50 kDa and glass particle sizes between 63 and 125 μm. Cements prepared with glass formulation $a = 0.125$ and $b = 0.000$ were analyzed after immersion in simulated body fluid; they presented a surface morphology consistent with a calcium phosphate coating and a Ca/P ratio of 1.55 (similar to calcium-deficient hydroxyapatite). Addition of starch to the cement formulation induced partial degradability after 8 weeks of immersion in phosphate buffer saline containing α-amylase. Micro-computed tomography analysis revealed that the inclusion of starch increased the cement porosity from 35% to 42%. We were able to produce partially degradable Al-free glass-ionomer bone cements with mechanical performance, bioactivity and biodegradability suitable to be applied on non-load bearing sites and with the appropriate physical characteristics for osteointegration upon partial degradation. Zn release studies (concentrations between 413 μM and 887 μM) evidenced the necessity to tune the cement formulations to reduce the Zn concentration in the surrounding environment.

1. Introduction

Wilson and Kent created the first glass-ionomer cement (GIC), in the early 1970s [1]. GICs are prepared through the mixing of a glass powder, usually a calcium fluoroaluminosilicate, with poly(acrylic acid) (PAA) and water. The curing reactions occur in two phases designated as gelation and maturation [2]. During gelation the acidic PAA attacks the glass particles at their basic sites, promoting the release of cations, e.g. 5-coordinated and 6-coordinated aluminum (Al) in the ionic form Al^{3+}, Ca^{2+}, etc., from the glass to the cement matrix. This process is followed by the maturation phase that includes the leaching of covalently bounded 4-coordinated Al (slower process due to its more stable position in the glass structure) and the ionic cross-linking of the PAA chains by the leached cations. These two cement-curing phases generate the GIC structure, a composite of cross-linked PAA reinforced with the reacted glass particles [2–6].

The usage of this type of cements is widespread within the dentistry field. This is mainly supported by the GIC's unique properties, namely, its strong adhesion to the hydroxyapatite present in dentin and its anti-cariogenic potential [1,7–9]. Initial drawbacks of conventional GICs comprised: sensitivity to moisture during initial hardening and poor mechanical properties, among others. Optimization of their formulations resulted in conventional and modified GICs (e.g. resin-modified GICs) with enhanced behavior [10–12].

Some GIC formulations were designed as cements for bone and otological surgeries. In the case of bone, several in vivo studies [13,14] reported the inhibition of bone mineralization and osteoid formation. It was also shown that Al accumulates in different tissues far from the implantation sites. These observations were similar to the ones reported for patients subjected to renal dialysis with Al-contaminated dialysates [14]. This type of body responses is known to induce Al-related osteomalacia. Additionally it has been reported that Al leached from GIC formulations was responsible for a reported fatal human Al-encephalopathy [15].

In order to overcome the Al deleterious toxic effects in biological tissues, a series of studies have been reported targeting the substitution of Al in the glass formulations. Alternative compositions, where Al is substituted by Zn, have been initially proposed by Darling et al. [16]. More recently, a series of studies [17–21] were dedicated to substitute Al from the cement formulation. The recently developed

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Zn-based cement formulations produce a significantly stronger adhesion to bone when compared with the Zn-free compositions [22]. These results indicate that Zn-based glasses can be used for the preparation of cements with an enhanced capacity to adhere to bone. A relevant drawback is the Zn cytotoxicity, although, the higher bone adhesion capacity allows the reduction of the concentration of the cytotoxic component, i.e. Zn, in the final cement. Additionally, in vitro studies have demonstrated that a low concentration of Zn in the cell culture medium can be beneficial for osteoblasts' proliferation [23]. In fact, cytotoxicity is only observed at a Zn concentration of ≥ 400 μM [22].

The potential benefits of substituting Al for Zn in the GIC formulations lead Towler and co-workers to test the cement forming ability of Zn-based glass particles (Al-free) of the ternary system calcium–zinc–silicates [19] and quaternary system calcium–strontium–zinc–silicates [20,21]. Al field strength is the basis of its intermediate character in the glass structure. Zn has also an intermediate character being a valid alternative to Al, although, the substitution of Al for Zn in the glass composition can lower significantly the GIC mechanical performance [16,24]. The Al^{3+} trivalent nature makes it highly efficient in cross-linking the polymeric chains. Griffin et al. [25] showed that Al- and phosphate-containing cement formulations exhibit a lower polymeric cross-linking due to the competing role of phosphates and carboxylates towards Al. These studies suggest that Al has a critical role in PAA cross-linking and, subsequently, in the cement mechanical properties.

Towler et al. [18–21] found that Zn-based glass compositions were able to produce cements of acceptable mechanical performance. These glass formulations always included low calcium and strontium fractions (cumulative values below 0.16) limiting the glass reactivity towards the PAA. A successful Al-free cement formulation should consider a compensation of the relevant role of Al in the PAA cross-linking. A possible methodology is to augment the role of the other glass modifier cations (e.g. Ca^{2+}, Sr^{2+}, and Mg^{2+}) in the cross-linking of PAA, through the increase of their concentration in the glass particles, an alternative herein explored.

In general, this study aims to improve the GIC formulation using: 1) the increase of the glass basic sites (i.e. higher concentration of Ca^{2+}, Sr^{2+}, and Mg^{2+} sites), in order to improve the glass reactivity towards PAA and enhance the GIC mechanical behavior; 2) the inclusion of higher fractions of CaO, SrO or MgO to improve the GIC in vitro bioactivity; 3) it is expectable that the type of divalent cations (Group II) included in the glass formulations (i.e. Ca^{2+}, Sr^{2+} and Mg^{2+}) will influence the cement final properties (e.g. mechanical behavior, etc.); and 4) the addition of starch to the cement formulation improves the GIC biodegradability creating a partially degradable bone cement.

2. Materials and methods

2.1. Glass synthesis

Zinc silicate glass formulations were already tested for their GIC forming ability by other authors [18–21], although, usually, high concentration of Zn (up to 53 mol%) and low-concentration of Group II cations (cumulative ≤16 mol%) were used. In this work we intend to evaluate the use of glasses with lower Zn concentration (approx. 30 mol%) and higher Group II cation concentration (approx. 25 mol%) for the formulation of GICs.

Glass formulations (G*x*) of general formula $0.340SiO_2{:}0.300ZnO{:}(0.250\text{-}a\text{-}b)CaO{:}aSrO{:}bMgO{:}0.050Na_2O{:}0.060P_2O_5$ (where a and $b = 0.125$ or 0.000) were prepared by melt quenching using appropriate proportions of glass precursors (Table 1). For this purpose, silica (Merck), zinc oxide (Sigma), magnesium oxide (Sigma, 98%), calcium carbonate (Sigma, 99%), strontium carbonate (Sigma, 98%), sodium hydrogen carbonate (Riedel de-Haen, 99.7%) and diammonium hydrogen phosphate (Sigma, 98%) were grounded with a pestle and mortar, transferred to a crucible and fired to 300 °C to release ammonia, to 650 °C to allow the release of carbon dioxide and to 1300 °C to produce the melt.

Table 1
Composition (molar fraction) of the synthesized glass formulations (G*x*).

Composition	Samples					
	G1[a]	G2	G3	G4	G5	G6
SiO_2	0.340	0.340	0.340	0.340	0.340	0.340
ZnO	0.300	0.300	0.300	0.300	0.300	0.300
MgO	0.250	–	–	0.125	–	0.125
CaO	–	0.250	–	0.125	0.125	–
SrO	–	–	0.250	–	0.125	0.125
Na_2O	0.050	0.050	0.050	0.050	0.050	0.050
P_2O_5	0.060	0.060	0.060	0.060	0.060	0.060

[a] G1 formulation did not produce a homogeneous melt at temperatures of up to 1350 °C.

Glass blocks were immersed in liquid nitrogen and grounded with a pestle and mortar. The glass particles were separated by size using an analytical sieve shaker (Retsch AS200) for 5 min at 60 rpm. With this procedure it was possible to collect three different fractions (with particle sizes of <63 μm, between 63 and 125 μm and between 125 and 250 μm) for each glass composition.

2.2. Cement preparation

2.2.1. Evaluation of the effect of different PAA molecular weights and glass particle sizes on the GIC mechanical performance

Cements (C*x*) were prepared by mixing the glass powder with PAA and water at an appropriate proportion (55:21:24 by mass). Upon mixing, the cement pastes were shaped in a Teflon mold to generate cylindrical specimens of 6 mm in diameter and 11 mm in height. Different fractions of glass particle sizes (<63 μm, 63–125 μm and 125–250 μm) and a series of PAA molecular weights (M_w of 50 kDa, PolySciences; 450 kDa, Sigma-Aldrich; and 1250 kDa, Sigma-Aldrich) were evaluated.

2.2.2. Adding starch to the composition that presented higher mechanical performance

The cement formulation (prepared under Section 2.2.1) that presented higher mechanical performance was modified to include corn starch (Sigma) to enhance its biodegradability. Starch weight percentages of 5% and 25% were tested. All the cement pastes were shaped in a Teflon mold as described in Section 2.2.1.

2.3. Glass and cement characterization

2.3.1. X-ray diffraction

The crystalline/amorphous state of the synthesized glass formulations was evaluated by X-ray powder diffraction (XRD). Diffractograms were collected on a Bruker D8 Discover, operating with Cu Kα radiation, in θ/2θ mode, between 6° and 70°, with a step increment of 0.04° and an acquisition time of 1 s per step.

2.3.2. Fourier transform infrared spectroscopy

The Fourier transform infrared (FTIR) spectra of the glasses and cements were collected using KBr (Sigma, 99%+) pellets on a Shimadzu IR-Prestige 21 spectrometer under transmittance mode, between 4400 and 400 cm^{-1}, using a resolution of 4 cm^{-1} and 32 scans.

2.3.3. Mechanical testing

The developed cement formulations were mechanically tested under compression loading on an Instron 5540 (Instron, USA) using a 1 kN load cell and 2 mm/min of crosshead speed. Six cylindrical specimens of each formulation were tested 1 day after preparation.