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Development of novel strontium containing bioactive glass based calcium phosphate cement

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ABSTRACT

Objective. The aim of this study was to investigate the effect on properties of increasing strontium substitution for calcium in bioactive glasses used as precursors for novel calcium phosphate cements.

Methods. Glasses were produced by progressively substituting strontium for calcium. Cements were prepared by mixing the glass powder with $Ca(H_2PO_4)_2$ powder with a 2.5% solution of Na_2HPO_4. Setting times and compressive strength were measured after 1 h, 1 day, 7 days and 28 days immersion in Tris buffer solution. X-ray diffraction (XRD), Fourier transform infrared spectroscopy and radiopacity were measured and crystal morphology was assessed using scanning electron microscopy.

Results. A correlation between the phases formed, morphology of the crystallites, setting time and compressive strength were analyzed. Setting time increased proportionally with strontium substitution in the glass up to 25%, whereas for higher substitutions it decreased. Compressive strength showed a maximum value of 12.5 MPa and was strongly influenced by the interlocking of the crystals and their morphology. XRD showed that the presence of strontium influenced the crystal phases formed. Octacalcium phosphate ($Ca_8H_2(PO_4)_6{\cdot}5H_2O$, OCP) was the main phase present after 1 h and 1 day whereas after 28 days OCP was completely transformed to strontium-containing hydroxyapatite ($Sr_xCa_{(10-x)}(PO_4)_6(OH)_2$, SrHA). Radiopacity increased proportionally to strontium substitution in the glass.

Significance. A novel method to develop a bone substitute forming in vitro SrHA as a final product by using a bioactive glass as a precursor was shown. These novel injectable bioactive glass cements are promising materials for dental and orthopedic applications. Further in vivo characterizations are being conducted.

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1. Introduction

1.1. Calcium phosphate cements

Calcium phosphate cements (CPCs) are bone grafting materials obtained by mixing one or several reactive calcium phosphate salts with an aqueous solution to form a self hardening paste. These cements are osteoconductive, possess molding capabilities and easy handling properties. They can be injected into bone defects where they set intimately adapting to the bone cavity. They possess sufficient compressive strength when compared to trabecular bone [1], are non-cytotoxic and have both the chemical composition and an X-ray diffraction pattern similar to those of bone [2]. Poor mechanical properties are the main disadvantages, as the resulting cement is weak under tensile forces [3] and as such they can only be used in combination with metal implants or in non-load bearing applications. They lack macroporosity and as degradation takes place from the external surface, rapid bone ingrowth into the material is impeded. The calcium phosphate salts used as reactive precursors are restricted by their stoichiometry, and therefore alterations of CPCs compositions are limited by the salts used.

1.2. Novel bioactive glass based calcium phosphate cement

Recently a novel injectable bone substitute material has been developed [4]. A bioactive glass (BG) is used as one of the reactive precursor to develop a novel CPC. BGs are amorphous solids produced from a SiO_2–P_2O_5–CaO–Na_2O system that in contact with physiological fluids form an apatite like layer on their surface allowing bone bonding through interaction with collagen fibrils [5]. BGs are commercially available as bone substitute materials and remineralizing agents in toothpastes [6]. As bone substitutes these materials lack of desirable mechanical properties. They are non-injectable and like other granular bone substitutes they are susceptible to deformation forces until a bond with surrounding tissues is formed. The use of BG as a precursor in CPCs has been shown to improve its properties and overcome the drawbacks of the current CPCs. The BG is a source of Ca^{2+} and PO_4^{3-} ions that react with the $Ca(H_2PO_4)_2$ salt to form hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$, HA). Using BG introduces the silicate phase which is a potential site for crystal nucleation [7], leading to a more rapid nucleation than conventional CPCs. Their dissolution in body fluids is correlated to cell mediated and pH dependent mechanisms, thereby undergoing faster resorption rates compared to CPCs. Their dissolution products like soluble silica and calcium ions stimulate osteogenic cells to produce bone matrix [8]. The setting time, strength and resorption rate can be improved by altering the glass composition, with no stoichiometric restriction unlike conventional CPCs. A recent animal study using an ovine model demonstrated that this novel CPC is osteoconductive and successfully osseointegrates with the host bone. It shows a higher degree of osseointegration and new bone formation when compared with a commercial CPC [9].

1.3. Strontium and its previous uses in CPCs and bioactive glasses

In certain applications, it is desirable to deliver a supply of therapeutic ions in the defect site or to produce substituted apatite phases. Among the bivalent cations that can replace Ca^{2+} in the structure of HA, Sr^{2+} has attracted a remarkable interest for its biological role. Sr^{2+} is present in the mineral phase of the bone, especially at the regions of high metabolic turn-over [10]. Addition of Sr^{2+} in biomaterials is beneficial because it has been shown to stimulate cell replication of pre-osteoblasts causing an increase in the rate of new bone formation. Sr^{2+} has also been shown to inhibit osteoclast differentiation and activity [11]. Thus, it is reasonable to expect that its presence in bone substitute materials may give better results in terms of biocompatibility and osseointegration. Sr^{2+} also adds a degree of radiopacity to the material due to its high atomic number, allowing the implanted material to be observed radiographically [12]. To date, the use of strontium carbonate appears the most suitable choice to obtain a sufficient degree of radiopacity in conventional CPC [13]. In previous works, addition of Sr^{2+} in CPCs has been achieved via different methods: (1) producing Sr-substituted salts as the powder starting material [14,15]; (2) by adding a separate Sr-containing powder as $SrHPO_4$ [16] or $SrCO_3$ [12,17]; (3) synthesizing Sr-substituted HA ($Ca_{(10-x)}Sr_x(PO_4)_6(OH)_2$) by a wet chemical route [18]; (4) adding soluble Sr^{2+} salts to the liquid phase used to start the cement reaction [19]. However, this has been shown to have deleterious effect on the setting reactions of CPC [16]. Therefore, a more efficient way is to introduce the Sr^{2+} ion in the glass structure enabling the beneficial effect of the ion without adversely affecting the cement properties. Because of their chemical similarity in terms of charge and ionic radius, Sr^{2+} for Ca^{2+} substitution in BG can be utilized to develop a new glass composition with improved regeneration capability and bioactivity. In vivo bioactive response of a strontium-containing BG is greater due to the biological effect of Sr^{2+} on cells and its slightly larger radius than Ca^{2+}, which expands the glass network and increases ion dissolution rates [20]. Therefore supersaturation of body fluids with Sr^{2+}, Ca^{2+} and PO_4^{3-} will occur faster forming the mixed Ca-Sr HA more quickly. Full substitution of Sr^{2+} for Ca^{2+} does not result in any decrease in cell proliferation or increased toxicity [21].

1.4. Aim

In this study a series of Sr^{2+} containing BGs were designed and synthesized to produce a range of CPCs by a novel route. The aim of this study was to develop, as the end product of the cement, a *n*Sr-HA and investigate the effect of Sr^{2+} on the physical and chemical properties of the cement.

2. Materials and methods

A previously studied glass with the composition 42.00SiO_2–4.00P_2O_5–39.00CaO–15.00Na_2O (mol.%) was selected [4]. In all the compositions the network connectivity was kept at 2.00 in order to maintain the same silicate Q structure in the glass network [22]. Sr^{2+} was substituted for