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Role of glass structure in defining the chemical dissolution behavior, bioactivity and antioxidant properties of zinc and strontium co-doped alkali-free phosphosilicate glasses

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ABSTRACT

We investigated the structure–property relationships in a series of alkali-free phosphosilicate glass compositions co-doped with Zn^{2+} and Sr^{2+}. The emphasis was laid on understanding the structural role of Sr^{2+} and Zn^{2+} co-doping on the chemical dissolution behavior of glasses and its impact on their in vitro bioactivity. The structure of glasses was studied using molecular dynamics simulations in combination with solid state nuclear magnetic resonance spectroscopy. The relevant structural properties are then linked to the observed degradation behavior, in vitro bioactivity, osteoblast proliferation and oxidative stress levels. The apatite-forming ability of glasses has been investigated by X-ray diffraction, infrared spectroscopy and scanning electron microscopy–energy-dispersive spectroscopy after immersion of glass powders/bulk in simulated body fluid (SBF) for time durations varying between 1 h and 14 days, while their chemical degradation has been studied in Tris–HCl in accordance with ISO 10993-14. All the glasses exhibit hydroxyapatite formation on their surface within 1–3 h of their immersion in SBF. The cellular responses were observed in vitro on bulk glass samples using human osteosarcoma MG63 cell line. The dose-dependent cytoprotective effect of glasses with respect to the concentration of zinc and strontium released from the glasses is also discussed.

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1. Introduction

Since the chemical degradation of multi-component glasses is strictly related to their atomic and molecular structure [1,2] the design of bioactive glasses able to stimulate specific cellular responses at the molecular level requires a thorough understanding of the relationship between their atomic/molecular structure and dissolution behavior. In fact, it has been well established that the ionic dissolution products are key to understand the behavior of their parent inorganic materials in vitro and in vivo, especially in the context of tissue engineering applications [3]. This relationship becomes more important when functional ions (e.g. Sr^{2+}, Zn^{2+}, F^{-}) are incorporated into the glasses with the aim of enhancing their biological efficacy, because these ions interact with and modify the phosphosilicate glass matrix, thus affecting the dissolution behavior of the resulting glass compositions. Therefore, it is of paramount importance to understand the influence of these functional ions on the structure and bioactivity of glasses so as to design glass compositions with controlled chemical dissolution and ion release rates.

Significant efforts have been made both to unearth the influence of functional ions on the structure of bioactive glasses [1,2,4–11] and to study their influence on the chemical dissolution behavior of glasses [12–19]. However, few attempts have been made to elucidate the correlation between the structural role of these functional ions and the chemical degradation and bioactivity of glasses [20–23]. Zinc and strontium are two such functional ions, the biological importance of which has been well documented in the literature [15,24–29]. While zinc is the most abundant trace metal in the human organisms (after iron), strontium

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content in the human skeleton is only 0.335% of the calcium content. Despite being present in trace amounts, both these ions play essential roles in the chemistry of bone regeneration due to their ability to associate with large number of proteins and other growth factors which contribute to the physiological processes, including DNA synthesis and gene expression. Because of its beneficial effects [30–32], strontium attracted much attention as a drug for the management of osteoporosis in the 1950s. The biological role of strontium in the human body has been reviewed by Nielsen [30], while its incorporation and distribution in bone has been experimentally evaluated in rats, monkeys and humans by Dahl et al. [33]. Similarly, the role of zinc is not only confined to bone tissue engineering but has also been shown to play a crucial role in soft tissue engineering. For example, in bone regeneration, it directly activates aminoacyl-tRNA synthetase (a rate-limiting enzyme in the translational process of protein synthesis) in osteoblastic cells and stimulates cellular protein synthesis [23], while, in the context of soft tissue regeneration, it plays an important role in wound healing and skin regeneration [34]. For this reason, several studies describing the influence of zinc and/or strontium on various aspects of bioactive glasses and their properties have been reported in the literature in the last few years [4,7,12–15,23,29,35–41]. Further, most of the work on strontium and zinc co-doped bioactive glasses available in the literature has been published by Boyd and co-authors [16,17,38,42–45] in the CaO–SrO–ZnO–Na_2O–SiO_2 glass system.

The present study aims to define the structure–property relationships in a series of alkali-free phosphosilicate glass compositions designed in the glass-forming region of diopside ($CaO{\cdot}MgO{\cdot}2SiO_2$)–flouroapatite ($Ca_5(PO_4)_3F$)–TCP ($3CaO{\cdot}P_2O_5$) and co-doped with Zn^{2+} and Sr^{2+}. An attempt has been made to understand the structural role of Sr^{2+} and Zn^{2+} co-doping on the chemical dissolution behavior of glasses and its impact on their apatite-forming ability, osteoblast proliferation and antioxidant behavior. The relevance of this work relies on the novel and rational compositional designing concept in the context of the existing studies already reported in the literature, the majority of them focused either on 45S5 Bioglass® or on glass compositions inspired by it [13,16,29,35,36,46,47]. However, our recent studies have shown that alkali-incorporation in bioactive glasses decreases their apatite-forming ability during the initial 72 h of contact with body fluids due to the excessive release of sodium from the glasses [48,49], thus leading to apoptosis. With reference to the use of 45S5 Bioglass® in vivo, Vogel et al. [50] showed that this glass has good biological efficacy in cases where shorter healing periods are required (~1 month), but it may not be a good option for injuries requiring prolonged treatment. The alkali-free glasses investigated in this study present viable alternatives to 45S5-based glasses, with slower chemical degradation, controlled ion release and high thermal stability, which allow them to be used as potential materials for bone regeneration and tissue engineered scaffolds [51].

The advantages of the investigated alkali-free bioactive glasses over the standard Hench-type bioglass formulations include: (i) faster biomineralization rate in vitro [51]; (ii) lower solubility and degradation rates, resulting in stronger adherence of the deposited hydroxyapatite layer to the bioglass substrate [50,51]; (iii) enhanced cell viability and cell proliferation due to smaller pH changes [51]; (iv) excellent processing ability in aqueous media, enabling solid loadings that are more than twice those achieved with the 45S5 Bioglass® powders, and good colloidal stability of the suspensions [52,53]; (v) non-hindered densification of powder compacts, enabling full density of the glass matrix to be achieved before crystallization starts [52,53]; and (vi) stronger mechanical properties and enhanced mechanical reliability. Further, the present series of glasses have a very small tendency to crystallization at high temperatures and exhibit good densification levels and mechanical strength values irrespective of their amorphous nature, being potential candidates for the fabrication of scaffolds or fibers for tissue engineering applications which involve high temperatures [53,54].

In light of the above, a series of alkali-free glasses with various Zn^{2+}/Mg^{2+} and Ca^{2+}/Sr^{2+} ratios: (mol.%) (36.07–x)CaO–xSrO–(19.24–x)MgO–xZnO–5.61P_2O_5–38.49SiO_2–0.59 CaF_2 (x = 0–10) have been synthesized by melt–quench technique. The glass compositions have been labelled from ZS-2 to ZS-10 in accordance with the respective ZnO and SrO content (mol.%). For example: ZS-2 corresponds to 2 mol.% ZnO and 2 mol.% SrO; ZS-4 corresponds to 4 mol.% ZnO and 4 mol.% SrO). Table 1 presents the detailed compositions of glasses investigated in the present study. The structure of the as-obtained glasses has been investigated by molecular dynamics (MD) simulations as well as magic angle spinning–nuclear magnetic resonance (MAS–NMR), while the biodegradation of glasses has been investigated by their immersion in Tris–HCl and simulated body fluid (SBF). Furthermore, the influence of glass structure and the dissolution behavior on osteoblast proliferation and oxidative stress levels has been discussed.

2. Experimental

2.1. Synthesis of glasses

All the glasses were prepared by the melt–quench technique. Batches comprising the respective oxides and fluorides (in accordance with the chemical compositions of the glasses presented in Table 1) were melted in a Pt–Rh crucible at 1570 °C for 60 min. Detailed information about the raw materials used for batch preparation is provided in our recent publication [54]. The glasses were obtained in both bulk and frit form. The bulk glass was obtained by casting the glass melt in a preheated metallic mold and further annealing it at 700 °C for 1 h, while the frits were obtained by quenching the glass melt in cold water. The frits were dried and then milled using agate grinding balls in a high-speed planetary mill, resulting in fine glass powders with mean particle sizes of 10–20 μm (determined by the light-scattering technique; Coulter LS 230, Beckman Coulter Fullerton CA; Fraunhofer optical model). The amorphous/crystalline nature of the frits was confirmed by X-ray diffraction (XRD) analysis (Rigaku Geigerflex D/Max, Tokyo, Japan; C Series; Cu K_α radiation; 2θ angle range 10–60°; step 0.02° s^{-1}).

2.2. Structural characterization

2.2.1. Structural characterization of glasses

2.2.1.1. Molecular dynamic simulations. MD simulations of the ZS-0, ZS-4 and ZS-10 compositions were performed using an established shell-model potential, developed to model modified silicate glasses [55] and further adapted and employed to model a wide range of melt-derived bioactive glasses [8,56–59]. The approximate incorporation of the polarizability of oxide ions in this potential through a shell-model approach improves the representation of medium-range structural features, such as the Q^n distribution, compared

Table 1
Nominal glass compositions of the starting batches (mol.%).

Glass	CaO	MgO	SiO_2	P_2O_5	ZnO	SrO	CaF_2
ZS-0	36.07	19.24	38.49	5.61	0.00	0.00	0.59
ZS-2	34.07	17.24	38.49	5.61	2.00	2.00	0.59
ZS-4	32.07	15.24	38.49	5.61	4.00	4.00	0.59
ZS-6	30.07	13.24	38.49	5.61	6.00	6.00	0.59
ZS-8	28.07	11.24	38.49	5.61	8.00	8.00	0.59
ZS-10	26.07	9.24	38.49	5.61	10.00	10.00	0.59

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