



Modulation of strontium release from a tertiary borate glass through substitution of alkali for alkali earth oxide



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ABSTRACT

The effect of the substitution of Na_2O for SrO in a series of nine borate glasses was studied to understand the effect of alkali for alkali earth oxide substitution in the boron transition range. Glasses were analyzed for post-firing composition, density, glass transition, ^{11}B MAS-NMR and ion release in a simulated physiological condition (immersion in PBS at 37 °C over time points of 1, 7, 30 and 60 days). Post-compositional analysis revealed decreases in boron and sodium content during glass firing, and allowed for improvements in composition property relationships. Increased substitution of sodium resulted in decreases in glass density, glass transition, and non-bridging oxygen fraction in the glass. Strontium ion release kinetics were governed by Fickian diffusion and were not altered by the substitution of sodium for strontium in the glass. Boron ion release varied from pure Fickian diffusion controlled to a parabolic release demonstrating precipitation with high sodium contents.

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1. Introduction

Bioactive glasses have been used in a variety of biomedical applications due to their ability to: (a) integrate with surrounding tissue, (b) fill defect or voids, (c) guide tissue regeneration (d) release therapeutic inorganic ions [1]. These materials have been particularly successful in the field of hard tissue engineering where they have been shown to support the remineralization of dentin as well as the regeneration of bone tissue [2]. This remineralizing effect is believed to be due in part to high local mineral content resulting from network dissolution, as well as the ability of certain therapeutic inorganic ions to alter local cellular behavior [1–4]. Therapeutic inorganic ions from bioactive glass dissolution products have also been shown to be beneficial in soft tissue applications, such as the release of copper ions, resulting in altered growth factor expression and improved angiogenesis [5,6].

Strontium is a therapeutic inorganic ion of particular interest in the field of bone regeneration. Strontium ions having been shown to effect bone cell metabolism of both osteoblasts and osteoclasts to elicit an increase in bone mineralization [7,8]. This therapeutic effect on bone metabolism has been shown to occur at both the systemic level (altering hormonal pathways which control bone metabolism) and at a local level through direct cell stimulation [7,9]. Due to its ability to alter bone metabolism in the local environment strontium has potential

application for local release from biomaterials [10]. Furthermore it has been shown to alter cell metabolism at low doses (8.8 mg/L), with a large therapeutic window increasing its ease of utilization [7].

While glass dissolution byproducts may be beneficial for tissue regrowth, rapid dissolution and burst release from bioactive glasses can have a toxic effect or compromise mechanical stability at the implant site [1]. For example Fu et al. found that borate ions released for bioactive glasses resulted in both decreased proliferation and osteogenic potential (assessed by ALP assay) of murine MLO-A5 cells in vitro [11]. Reports of losses in compressive strength (associated with glass degradation) following incubation in simulated body fluid can vary from 40 to 80% depending on the composition of the glass [12]. Further to losses of mechanical strength, borosilicate glass designed for rapid dissolution and conversion into hydroxyapatite can decrease DNA synthesis up to 78% in *in vitro* conditions, while a slow conversion analog glass showed no inhibition [13]. A balance of network stability to reduce toxicity and degradation to allow tissue integration is often sought through modification of the glass network, this however requires an understanding of composition structure relationships.

Recent research into borate based bioactive glasses has shown highly tailorabile degradation rates. For example in the borate glass series investigated by Hasan et al. the total mass loss varied from 2 to 22% over 21 days through variation of glass composition [14]. A similar mass loss range of 3–20% was reported in a single week in the work of Abdelghany et al. [15]. However, for borate based glass systems our understanding of the underlying composition-structure-property relationships lags behind that of other glass systems, partially due to the low

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fraction of glass science studies which focus borate glasses (2% of US publications while 20% focused on silicate glasses between 2007 and 2013) [16]. For binary borate glasses composition-structure-relationships have been well studied through the use of NMR, Raman and infrared spectroscopy for alkali or alkali earth containing glasses [17–22]. These studies have focused primarily on the generation of four fold coordinated boron or non-bridging oxygens through the addition of modifying oxides and their effect on the glasses density, thermal, and optical properties [17,20–22]. These structural studies have explained the basis of the borate anomaly with a change in borate coordination occurring at higher modifier contents, and non-bridging oxygen formation at lower modifier contents. This change in structural role of glass modifiers results in a non-linear, parabolic, relationship between modifier content and glass properties such as density and glass transition [20]. Furthermore mixed alkali effects have been investigated in tertiary borate glasses and have been shown to have a dramatic effect on the transition region changes the region of inflection for glass properties [23]. The effect of mixtures of alkali and alkali earth metals however has not been as well studied for its effect on glass degradation kinetics.

Bioactive borate glasses remain of interest despite these difficulties due to their high variability in dissolution rates making them highly tailorabile, providing potential for use in the delivery of therapeutic ions. This study aims to investigate the therapeutic ion release potential of a tertiary borate glass through the substitution of sodium (an alkali oxide) for strontium (an alkali earth oxide) and study the effect of this substitution on glass structure, and stability. This was undertaken through fabrication of a series of tertiary glasses in which sodium oxide (0–16% molar fraction) was substituted in for strontium oxide (30–14% molar fraction) while maintaining boron oxide concentration constant (70% fraction). This glass was investigated to elucidate structure, stability, density, and glass transition. Post-synthesis composition analysis was performed to allow for more accurate composition structure and composition property relationships to be investigated.

2. Methods

2.1. Glass synthesis

Nine glasses were synthesized through rapid quenching of oxide melts according to the compositions listed in Table 1. Materials were weighed out and transferred into HDPP jars, mixed in a dry blender for 1 h, then packed into Pt/Rb crucibles. Packed crucibles were placed in a Carbolite high temperature furnace at room temperature, then the temperature was raised by 50 °C/min to 500 °C, held for an hour to calcinate and ramped by 50 °C/min to 1100 °C. The final melting temperature was held for an hour before quenching between stainless steel plates. The resulting glass was ground using a planetary ball mill (Pulverisette 7) and sieved to retrieve sub 45 µm powder (ASTM standard sieves, Cole Parmer). Particle size distribution was verified through

Table 1

Glass compositions by molar fraction of pre-fired material, and actual compositions revealed in compositional analysis (molar percentage and standard deviation).

Glass	Theoretical compositions (molar %)			Final compositions (molar % (SD))		
	B ₂ O ₃	SrO	Na ₂ O	B ₂ O ₃	SrO	Na ₂ O
BSr ₃₀	70	30	0	67.5 (0.7)	32.5 (0.7)	—
BSr ₂₈	70	28	2	68.4 (0.5)	31.4 (0.5)	0.2 (0.01)
BSr ₂₆	70	26	4	68.9 (0.8)	27.6 (0.9)	3.5 (0.1)
BSr ₂₄	70	24	6	67.8 (0.6)	25.4 (0.5)	6.8 (0.1)
BSr ₂₂	70	22	8	68.5 (0.7)	23.8 (1.0)	7.7 (0.3)
BSr ₂₀	70	20	10	69.2 (0.2)	21.1 (0.1)	9.7 (0.1)
BSr ₁₈	70	18	12	69.7 (0.8)	18.0 (0.1)	12.3 (0.03)
BSr ₁₆	70	16	14	66.0 (0.5)	17.3 (0.8)	16.7 (0.4)
BSr ₁₄	70	14	16	67.4 (0.1)	15.5 (0.9)	17.1 (0.2)

laser diffraction of a wet suspension using a Mastersizer 300 model laser diffraction particle size analyzer using distilled water as the dispersant.

2.2. Post-synthesis composition verification

Glass digests were performed in triplicate on all 9 glass compositions using 50 mg of glass dissolved in 10 mL of ultrapure hydrochloric acid (37% Ultra Trace, Sigma Analytical) in an HDPP digest vial. Each vial was capped, gently agitated, and heated to 35 °C for 2 h to ensure full dissolution of the glass powder. Glass digests were then diluted in 2% HCl for ICP analysis of B, Sr and Na content. Elemental analysis of glass digests and extracts was performed by ICP-AES on a Perkin Elmer Optima 8000 using a 2% hydrochloric acid suspension media, nitrogen carrier gas and an argon flame. Calibration curves were produced using Perking Elmer pure ICP standards. All samples were measured in triplicate and recorded as the mean of 3 readings. Actual (post-firing) compositions were used for all composition structure and composition property analysis.

2.3. X ray diffraction analysis

XRD was performed on all glass samples to verify amorphyticity using a Bruker AXS D8 diffractometer (Department of Physics, Dalhousie University, Canada). The system utilized Cu-K α radiation, a Göbel mirror, a Vantec-2000 area detector, and a copper target. Samples were measured over a scattering angles range from 10° < 2θ < 110° (step size: 0.033°), with a step time of 0.5 s.

2.4. Structural characterization

Network structure of the nine glass compositions was investigated using ¹¹B MAS NMR experiments. NMR measurements were acquired on a 16.4 T Bruker Avance NMR spectrometer (¹¹B Larmor frequency = 224.67 MHz) using a 2.5 mm HX probe head operating in single resonance mode. ¹¹B parameters were calibrated on solid NaBH₄, which was also used as an external chemical shift reference (−42.1 mg/L relative to BF₃·Et₂O). Two spinning speeds were acquired for each sample: 25 kHz (32 transients acquired per sample) and 10 kHz (4 transients acquired per sample). A 0.56 µs pulse was used for all experiments, corresponding to a pulse angle of roughly 15°. Spin lattice relaxation times were determined by saturation recovery and ranged from 6 to 7 s. Five times this value was used at the pulse delay. As the stator gives a considerable boron background, the spectrum of an empty rotor was also acquired under identical conditions at each spinning speed. This spectrum was phased and adjusted for intensity before being subtracted from the experimental spectra.

2.5. Glass density

Density measurements were performed using a gas pycnometer (Micromeritics AccuPyc II 1340) with a helium purge gas, and 1 cm³ chamber insert, packed with approximately 0.75 g of glass powder. Three glass samples were analyzed for each composition with measurements taken as the mean of 10 readings.

2.6. Thermal analysis

Glass transition temperatures were determined for each of the nine glasses through differential scanning calorimetry using a TA Instruments Q200 DSC (TA instruments, Grimsby, Canada) fitted with an S type thermocouple. 30 mg glass samples were heated in platinum pans at a heating rate of 10 °C/min from 100 to 800 °C. Glass transition temperatures were determined as the onset of inflection as determined using Q series software (TA Instruments, Grimsby, Canada).

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