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# Linear release of strontium ions from high borate glasses via lanthanide/ alkali substitutions

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ABSTRACT

The effect of increasing substitutions of $La_2O_3$:$Na_2O$ on the structure ($^{11}B$ MAS NMR) and properties, specifically strontium (Sr) ion release from five quaternary borate glass compositions ($B_2O_3$–SrO–$Na_2O$–$La_2O_3$) was studied. To examine component ion release, samples were extracted under simulated physiological conditions at 37 °C for five extraction time points (24, 72, 168, 336 and 720 h). A linear release profile for strontium was provided by composition LB102 ($70B_2O_3$–20SrO–$6Na_2O$–$4La_2O_3$) for up to 720 h. $^{11}B$ MAS NMR was used to investigate the impact of $La_2O_3$:$Na_2O$ substitution on the boron structure and speciation. Substitutions appeared to have minor effects on borate speciation, with the only change being a decrease in the proportion of $BO_4$ at maximum $La_2O_3$ loading ($70B_2O_3$–20SrO–$10La_2O_3$). These data further demonstrate the possible utility of high boron glasses as controllable degradable materials for the delivery of therapeutic metal ions, such as strontium.



## 1. Introduction

The utilization of specific therapeutic metallic ions (TMIs) has become increasingly prevalent in the treatment of a variety of diseases and metabolic disorders [1]. One example relating to the successful deployment of metallic ions to treat pathological processes is the use of strontium (Sr) as an anti-osteoporotic agent for post-menopausal women [2]. In this context, it has been demonstrated, through multiple clinical studies, that strontium ranelate "…demonstrates broad spectrum safety and efficacy in reducing the risks of both vertebral and nonvertebral (including hip) fractures in a wide variety of patients, and should be considered as a first-line option to treat women at risk of osteoporotic fractures, whatever their age, the severity of the disease, and their risk factors." [3,4]. However, in a broader sense, much of our knowledge relating to the therapeutic effects of metallic ions is concerned with *systemic* levels and concomitant physiological (beneficial/adverse) responses rather than their *local* levels and associated effects. Appropriately, there is increasing interest in the local delivery of TMIs from functional implants to mediate desired host responses [1,2,5]. This philosophy is capacitated by a number of features; a primary benefit of TMIs, as summarized by Mourino et al. and Hoppe et al. is that many (for example gallium, zinc, and silver) [5,6] have (i) broad spectrum capabilities relating to the modulation of biological functions via interactions with other ions, (ii) may bind to macromolecules such as enzymes and nucleic acids modulating certain cellular processes, and (iii) can influence ion channels and signaling pathways [5,7]. However, such therapeutic effects are species, dose and duration specific [2]. Crucially, in the context of local delivery of TMIs from functional implants, controlling these factors is critical so as to obtain the desired biological response while avoiding adverse ion accumulation and local toxicity, which may result in unwanted immune and inflammatory responses [1,5,8].

From the pharmacological literature, it is clear that the concept of controlled release of any TMI from a functional implant will necessitate both, (i) the ability to control release at a target site and (ii) sustain delivery at an effective and safe concentration for a predetermined period of time [1,9,10]. Linear release (i.e. constant release) is desired since, in principle, it provides the best mechanism of temporal control over TMI release and therefore minimizes local fluctuations in concentration [11]. With respect to the latter, these fluctuations may lead to periods of under and over-dosing, a reduced time within the therapeutic window, and consequently a reduction in the lifespan of the therapeutic effect [9,11]. In the context of hard tissue augmentation, and in addition to the vectored delivery of TMIs to accelerate regeneration and healing, it is also crucial that the carrier material provides for controlled resorbability leading, ultimately, to its replacement with mature bone in the absence of any transient loss of mechanical properties [12]. In this context, glass materials are of particular interest as they provide for an almost infinite

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number of compositional design spaces, which may provide a broad range of desirable characteristics for bone augmentation [2,13].

Silica-based glasses (silicates being the most studied of all glass networks) [14] have shown constant Sr release profiles, however, none yet provide for completely resorbable characteristics in a fashion consistent with that required for clinical efficacy [12]. While there is a considerable literature related to Sr releasing glasses, limited evidence exists where they provide for; (i) linear release of TMIs and, (ii) linear release of TMIs from fully resorbable materials. With respect to the former, one example is of note; Murphy and coworkers [15], showed that a zinc silicate glass comprising $0.4SiO_2$–$0.3SrO$–$0.3Na_2O$ (mol%) provided constant release of therapeutic concentrations of Sr up to 30 days [15]. However, these zinc-silicates, by virtue of their composition and structure, cannot provide for complete resorbability. As an alternative approach, boron (B) based glasses are becoming increasingly attractive in biomedical applications, particularly as vitreous borate is fully degradable. Accordingly, high borates may provide an effective resorbable delivery matrix for localized/controlled release of TMIs [16–18]. Importantly, studies on borate glasses, while limited (i.e. less that 2% of glass research in the US relates to borate glasses [14]) have demonstrated a mechanistic basis for the control of properties, such as chemical durability, via composition and structure [19–23]. These mechanisms are attributed to the concentration dependent response of the B system to the addition of modifying cations, which ultimately vary with the magnitude of the modifiers charge and associated field strength [24]. With this as the backdrop we hypothesize that the inclusion of a rare earth element (REE) (i.e. lanthanum (La)) may provide a mechanism to stabilize a high borate glass and yield a biomaterial with appropriate resorption characteristic and linear Sr release kinetics for bone augmentation. While the precise role of REEs on borate glass structure has not been well defined, this hypothesis is on the basis that trivalent ions result in a more negatively charged local environment and as a consequence may have more pronounced structural effects on borate networks than alkalis [16,18,25,26].

## 2. Materials and methods

### 2.1. Glass synthesis

Six glass compositions (Table 1) were synthesized. Glasses were prepared by weighing appropriate amounts of the following analytical grade reagents (Sigma Aldrich, Canada): boron oxide, strontium carbonate, sodium carbonate and lanthanum (III) oxide. Each formulation was thoroughly mixed for 60 min to ensure a homogeneous mixture of reagents was obtained. Once homogenized, glass precursor blends were placed in 50 ml Pt crucibles (Johnson Matthey, Noble Metals, Pennsylvania) then placed in a furnace at room temperature. The precursor blends were heated (25 °C/min) to an initial dwelling temperature of 600 °C and held for 60 min. Subsequently the furnace was ramped (25 °C/min) to a final dwelling temperature of 1100 °C and held for 75 min. Each glass melt was then quenched between two stainless steel plates and the resulting glass was ground with a planetary micro mill (Pulverisette 7, Fritsch, Germany) then sieved to retrieve particles of <45 and 45–150 μm using ASTM E-11 compliant sieves (Cole Parmer, USA). Glasses were stored in glass scintillation vials under vacuum for subsequent analysis.

**Table 1**
Mol. fraction compositions of LB glass compositions.

| Glass designation | $B_2O_3$ | SrO | $Na_2O$ | $La_2O_3$ |
|---|---|---|---|---|
| LB100 | 0.70 | 0.20 | 0.10 | 0.00 |
| LB101 | 0.70 | 0.20 | 0.08 | 0.02 |
| LB102 | 0.70 | 0.20 | 0.06 | 0.04 |
| LB103 | 0.70 | 0.20 | 0.04 | 0.06 |
| LB104 | 0.70 | 0.20 | 0.02 | 0.08 |
| LB105 | 0.70 | 0.20 | 0.00 | 0.10 |

### 2.2. Characterization of glass powders

#### 2.2.1. Particular size analysis (PSA)

A Malvern mastersizer (MS) 3000 laser diffraction particle size analyzer was, as per manufacturers' instructions, used to determine the particle size distribution for each glass. Each glass powder was suspended in deionized water to obtain an obscuration value for the suspension between 5 and 8%. Each glass suspension was then measured using both a blue ($\lambda = 470$ nm) and red ($\lambda = 632.8$ nm) laser. Each glass suspension was measured 5 times ($n = 5$). Particle size distribution data is reported as the mean diameter D90, D50 and D10, which are particle diameters at 90%, 50% and 10% cumulative size, respectively..

#### 2.2.2. X-ray diffraction (XRD)

A Bruker D-8 Discover diffractometer equipped with a Vantec-500 area detector and a Cu target X-ray tube was used for XRD measurements. Powder specimens of each glass (<45 μm), were pressed into a square hollow steel wafer (dimensions) and scanned between $10° \le 2\theta \le 95°$ with a step size $2\theta = 0.02$.

#### 2.2.3. Differential scanning calorimetry (DSC)

DSC was performed using a simultaneous thermal analysis — STA 409 PC Luxx® (Netzsch-Geratebau-GMBH, USA). Powdered glass specimens of each glass ($n = 3$ per glass, <45 μm) were heated at 10 °C/min from 50 to 1000 °C. Specimens were weighed into platinum crucibles and had a mass no greater than 35 mg. The glass transition temperature ($T_g$), was determined based on the inflection point in the heat flow curve, determined using Proteus Analysis software (VERSION 5.1.1) and is reported as the average ± standard deviation (SD).

#### 2.2.4. Helium pycnometry

An AccuPyc 1340 helium pycnometer (Micromeritics, USA) equipped with a 1 $cm^3$ sample insert chamber was, as per manufacturer instructions, calibrated and used for density measurements. 0.7–0.8 g of powdered glass specimens of each glass ($n = 10$ per glass, 45–150 μm) was used. The results are reported as the average ± SD. Molar volume was calculated for each glass composition by $V = M/p$, where M is the molecular weight of each glass and p is the density.

### 2.3. Analysis using $^{11}B$ MAS NMR

$^{11}B$ magic angle spinning (MAS) NMR spectra were acquired on a 16.4 T Bruker Avance NMR spectrometer ($^{11}B$ Larmor frequency = 224.67 MHz) using a 2.5 mm HX probehead operating in single resonance mode. $^{11}B$ parameters were calibrated on solid $NaBH_4$, which was also used as an external chemical shift reference (−42.1 ppm relative to $BF3{\cdot}Et_2O$). 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. Peak heights, widths and integrations were measured using XWinNMR's native tools.

### 2.4. Quantification of metal ion release under simulated physiological conditions

0.1 g of each glass composition (45–150 μm) ($n = 3$) was immersed in 10 mL of tissue culture water (Sigma-Aldrich, Canada) using 15 mL polypropylene Falcon tubes [16,17,27,28]. Incubation periods of 24, 72, 168, 336 and 720 h were utilized. Each specimen was stored at 37 °C