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A preliminary investigation into the structure, solubility and biocompatibility of solgel SiO_2–CaO–Ga_2O_3 glass-ceramics

A.W. Wren [a, *], M.C. Jones [a], S.T. Misture [a], A. Coughlan [b], N.L. Keenan [a], M.R. Towler [c], M.M. Hall [a]

[a] Inamori School of Engineering, Alfred University, Alfred, NY 14802, USA
[b] School of Materials Engineering, Purdue University, West Lafayette, IN, USA
[c] Department of Mechanical & Industrial Engineering, Ryerson University, Toronto, Canada

HIGHLIGHTS

- A solgel derived glass-ceramic series was synthesized with 5 mol% Ga_2O_3 doped for the SiO_2 and CaO.
- Characterization included X-ray diffraction, thermal analysis and particle analysis methods.
- Materials released gallium (Ga), calcium (Ca), silica (Si) and caused an increase in pH over time.
- Antibacterial effects were observed when tested in *E. coli* and *S. epidermidis*.
- No significant reduction in cell viability was observed with material ionic dissolution species.

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ABSTRACT

The proposed study aims to synthesize gallium (Ga^{3+}) containing glass-ceramics *via* the solgel method and determine their solubility and biocompatibility. Three solgel derived glass-ceramics, two containing Ga^{3+} were synthesized by substituting 5 mol% Ga^{3+} for both Ca^{2+} (*Si-65*) and Si^{4+} (*Si-70*) and were compared to a Ga^{3+} free control (*control*). Glass transition temperatures (T_g) ranged from 641 to 660 °C for all materials with particle sizes ranging between 1.5 and 2.5 μm. Surface area analysis ranged from 45 to 55 $m^2\,g^{-1}$ and any changes in pH were determined over 0–14 days. Ga^{3+} ion release from *Si-65* peaked at 433 mg L^{-1} after 7 days, and *Si-70* peaked at 601 mg L^{-1} after 1 day. Both calcium (Ca^{2+}) and silica (Si^{4+}) were also released from each material. Antibacterial testing against *E. coli* and *S. epidermidis* revealed both bactericidal (maximum inhibition zone of 2.5 ± 0.3 mm) and bacteriostatic effects. The *control* material exhibited inhibition zones in both bacteria while bacteriostatic properties were found predominantly against *E. coli* with *Si-65* and *Si-70*. Cytocompatibility testing was conducted in L929 mouse fibroblasts and determined no significant reduction in cell viability with respect to the *control*, with minimal, non-significant reductions for *Si-65* and *Si-70*.

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1. Introduction

Since the invention of Bioglass®, bioactive glasses, have been investigated for a range of orthopedic applications as they exhibit excellent osteoconductive properties [1,2]. Controlled release of ionic dissolution products, in particular, concentrations of soluble silica (Si^{4+}) and calcium (Ca^{2+}) are known to be essential to the bioactive process [1]. This has led to investigators to synthesize novel bioactive glasses to improve bioactivity and/or antibacterial properties [3,4]. Employing solgel processing can lead to positive characteristics over melt quenching route, including lower processing temperatures, uniform phase distribution, new crystalline/non-crystalline materials [5], high surface area powders [6,7] and greater homogeneity [6] which yields glasses which cannot be easily prepared by melt quenching [7,8]. Studies on $70SiO_2$–$30CaO$ solgel glasses has previously been described by Vallet-Regi [9,10] et al. and Saravanapavan *et al* [11], which focused primarily on the synthesis and incubation of these glasses in Simulated Body Fluid (SBF), which presented positive signs of bioactivity [9–12].

* Corresponding author. Tel.: +1 607 871 2183; fax: +1 607 871 2353.
E-mail address: wren@alfred.edu (A.W. Wren).

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The addition of gallium (Ga^{3+}) to silicate glasses through solgel processing can be used to address problematic areas in orthopedics. Previous studies by Shruti et al. [13] on GaO_2 doped SiO_2–CaO–P_2O_5 solgel glasses presented positive surface reactions in SBF [13], whereas Bolis et al. reports that GaO_2 reduces apatite formation [14]. However, Ga^{3+} can also be incorporated to eradicate tumor cells and reducing the risk of infection post-surgery. Antibiotic overuse can promote multi drug-resistant strains of bacteria [15–17], such as MRSA (Methicillin Resistant *S. aureus*) which has resulted in the need for antibiotic free materials for treating persistent infection such as antibacterial ions (Zn^{2+}, Ag^{+}) [18–21] and compounds [22,23]. Ga^{3+} is an element that presents multi-therapeutic potential when incorporated into medical materials and although there is no specific biological role for Ga^{3+} in humans, it has been reported to present beneficial therapeutic effects when incorporated into materials used to treat disease/infection in humans. These disorders range from accelerated bone resorption, autoimmune disease and allograft rejection, certain cancers and infectious disease [24] in addition to treating hypercalcemia of malignancy and Pagets disease [24]. Ga^{3+} has also been used to suppress osteolysis and bone pain associated with multiple myeloma and bone metastases, in addition to being investigated as a treatment for osteoporosis [24]. Ga^{3+} physiological activity is cited as being due to its atomic similarities (electric charge, ionic diameter and coordination number [25]) with iron (Fe^{3+}), in particular, regarding protein and chelate binding [24]. Biochemically, the most important difference is that Ga^{3+} is irreducible under physiological conditions, whereas Fe^{3+} can be readily reduced to Fe^{2+}. This prevents Ga^{3+} from entering Fe^{2+} binding molecules and prevents it from participating in redox reactions and is known to be transported through blood plasma by the iron-transport protein transferrin. Ga^{3+} has a strong affinity for certain tissues such as bone and many tumors and accumulation of Ga^{3+} in tumors (lymphomas) is associated with large amounts of transferrin receptors (TF). However, bone tissue does not generally contain high concentrations of Fe^{3+} binding proteins and the mechanism of skeletal Ga^{3+} accumulation remains relatively unknown. Ga^{3+} accumulation in bone tissue has led to treating disorders such as multiple myeloma [24] and treating infection as Ga^{3+} is known to be able to disrupt bacterial metabolism [26–28] in species such as *M. tuberculosis* and *M. avium*, *S. aureus*, *E. coli*, *P. aeruginosa*, *MRSA* and *C. difficile* [26,29–31], which is also related to Ga^{3+} ability to enter microbes through their iron transport mechanisms which disrupts iron metabolism and DNA/protein synthesis [24].

Regarding this study, a CaO–Ga_2O_3–SiO_2 glass-ceramic series was prepared using the solgel processing. The effect of each materials structure and solubility was evaluated against common bacterium such as *E. coli* and *S. epidermidis*, in addition to a standard mammalian cell line (L929 mouse Fibroblasts) to evaluate any potential cytotoxicity.

2. Materials & methods

2.1. Glass-ceramic synthesis

2.1.1. Materials

Glass-ceramic samples were prepared using a solgel method based upon that described by Saravanapavan and Hench [11]. The following compounds were used to create CaO–SiO_2 and CaO–Ga_2O_3–SiO_2 gel glass-ceramics: TEOS ($Si(OC_2H_5)_4$), nitric acid (HNO_3), calcium nitrate tetrahydrate ($Ca(NO_3)_2{\cdot}4H_2O$), gallium nitrate hexahydrate ($Ga(NO_3)_3{\cdot}6H_2O$) (reagents, Fisher Scientific), and deionized (DI) water, according to Table 1 compositions. As TEOS needs an acid or base catalyst, the 2 N nitric acid (HNO_3) is added during sol preparation. The amount of HNO_3 is determined according to the following ratios: a molar ratio of H_2O/TEOS is 12:1 and a volume ratio of H_2O/HNO_3 is 6:1 [11].

Table 1
Composition of glass series (Mol. %).

	Composition			
		SiO_2	CaO	Ga_2O_3
Control	0% Doped	70	30	0
Si-65	5% SiO_2 Doped	65	30	5
Si-70	5% CaO Doped	70	25	5

2.1.2. Gel synthesis

The 2 N HNO_3 and the deionized water were stirred together in a Teflon beaker at room temperature for 5 min. $Si(OC_2H_5)_4$ was added over a 30-min period and the mixture was stirred for an additional 30 min to ensure homogeneity and complete hydrolysis. $Ca(NO_3)_2{\cdot}4H_2O$ and, where appropriate, $Ga(NO_3)_3{\cdot}6H_2O$, were then added and allowed to dissolve. $Ga(NO_3)_3{\cdot}6H_2O$ was added over a 5-min period to prevent rapid gelation, which reduces homogeneity. The sol was stirred for 1 h, followed by casting into sealed 38 mm polypropylene containers which had three 1 mm Ø holes in their tops to allow release of gases that evolved during drying (Fig. 1).

2.1.3. Solgel glass synthesis

Wet gels were dried and aged simultaneously in a programmable oven at 60 °C for 72 h. Aging and drying ensure complete gelation and solidification. Each material was stabilized in Al_2O_3 crucibles in a programmable oven according to the schedule in Table 2 [11]. X-ray diffraction was conducted on each glass (*Control*, *Si-65* and *Si-70*) prior to stabilization and each was determined to be amorphous (data not presented).

2.2. Sample preparation

Each glass-ceramic was ground to a fine powder using a gyromill (Glen Creston, UK) for initial characterization. For solubility and antibacterial testing, each material was tested in two forms, powder form and disc form, to determine if the increased dissolution of the individual particles in the powder form increases the antibacterial effect. Samples were produced and evaluated as follows:

- Powder form (1 m^2 surface area, $n = 3$)
- Solid pressed disc (4 mmØ × 1.3 mm, 1 m^2 surface area, $n = 3$)

To form discs, molds 4 mm Ø were filled with powder and pressed to form discs (1.3 mm thick). For ion release and pH

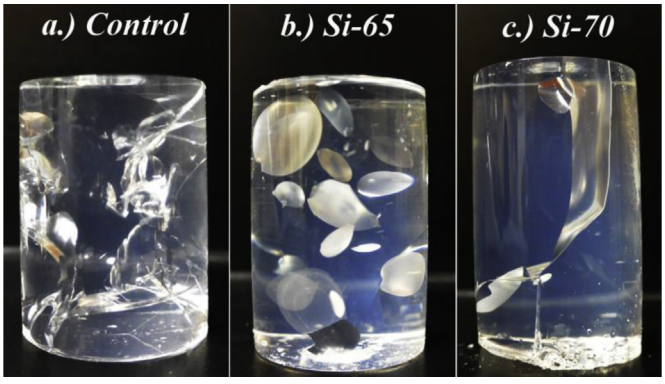

Fig. 1. Solgel glasses a.) *Control*, b.) *Si-65* and c.) *Si-70*.

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