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# Melt-derived bioactive glass scaffolds produced by a gel-cast foaming technique

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ABSTRACT

Porous melt-derived bioactive glass scaffolds with interconnected pore networks suitable for bone regeneration were produced without the glass crystallizing. ICIE 16 (49.46% $SiO_2$, 36.27% CaO, 6.6% $Na_2O$, 1.07% $P_2O_5$ and 6.6% $K_2O$, in mol.%) was used as it is a composition designed not to crystallize during sintering. Glass powder was made into porous scaffolds by using the gel-cast foaming technique. All variables in the process were investigated systematically to devise an optimal process. Interconnect size was quantified using mercury porosimetry and X-ray microtomography (μCT). The reagents, their relative quantities and thermal processing protocols were all critical to obtain a successful scaffold. Particularly important were particle size (a modal size of 8 μm was optimal); water and catalyst content; initiator vitality and content; as well as the thermal processing protocol. Once an optimal process was chosen, the scaffolds were tested in simulated body fluid (SBF) solution. Amorphous calcium phosphate formed in 8 h and crystallized hydroxycarbonate apatite (HCA) formed in 3 days. The compressive strength was approximately 2 MPa for a mean interconnect size of 140 μm between the pores with a mean diameter of 379 μm, which is thought to be a suitable porous network for vascularized bone regeneration. This material has the potential to bond to bone more rapidly and stimulate more bone growth than current porous artificial bone grafts.



## 1. Introduction

There is a clinical demand for artificial bone graft materials (bioactive scaffolds) that can stimulate bone regeneration by acting as temporary templates for vascularized bone growth. Applications are spinal fusions, non-union fractures of bones and other less common defects such as the Hills–Sachs defect in the shoulder and defects resulting from tumour removal. The scaffold should have an interconnected pore structure, with interconnected pore sizes that are greater than 100 μm, be resorbable and posses the ability to stimulate bone growth [1].

There are many porous bioceramic artificial bone graft products commercially available, usually calcium phosphates. Bioactive glass particles have been found to be more bioactive than synthetic hydroxyapatite in vivo [2]. Bioglass® 45S5 (46.1% $SiO_2$, 24.4% $Na_2O$, 26.9% CaO, and 2.6% $P_2O_5$, in mol.%) was the first material found to bond to bone [3] and is commercially available in powder form (e.g. Novabone Products LLC, Alachua, FL, USA). Bioactive glasses have excellent osteogenic properties due to their dissolution products stimulating gene up-regulation in osteoblasts [4,5]. Porous amorphous glass scaffolds have not been made from Bioglass® as it crystallizes to form a glass–ceramic when sintered [6], which greatly reduces its bioactivity. Glass–ceramic scaffolds based on 45S5 composition with an open pore structure have been produced by using sacrificial polymer foam templating, but compressive strength was less than 0.5 MPa, with ~85% porosity. An apatite layer was also not clearly formed until 4 weeks' immersion in SBF [7]. During scaffold production from glass particles, the particles must be sintered together and Bioglass® crystallizes during this process because it has a very narrow sintering window, which is the temperature gap between its glass transition temperature ($T_g$) and its onset temperature for crystallization ($T_{c\ onset}$). In order to sinter a glass by viscous flow sintering, the temperature must be well above $T_g$ but below the $T_{c\ onset}$. Crystallization reduces bioactivity of the Bioglass® and as bioactive glasses exhibit strongly surface nucleated crystallization, viscous flow sintering will be dramatically reduced if the glass crystallizes. As a result of the poor processing characteristics of the 45S5 glass, alternative routes were pursued for making bioactive glass scaffolds such as the sol–gel foaming method [8–10]. However, sol–gel glass may degrade too rapidly for certain applications where the bone will take a long time to regenerate.

The first amorphous melt-derived bioactive glass scaffold produced with a pore structure suitable for bone in-growth was developed by Fu et al. where the polymer foam replication technique was used with a glass composition 13–93 (54.6 mol.% $SiO_2$,

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22.1 mol.% CaO, 6.0 mol.% $Na_2O$, 7.7 mol.% MgO, 7.9 mol.% $K_2O$, 1.7 mol.% $P_2O_5$). The composition expanded the sintering window compared to 45S5 glass and allowed the glass to be sintered without crystallization. The scaffolds sintered well and established an interconnected pore network with pores in the range of 100–500 μm (~85% porosity) and achieved a compressive strength of 11 MPa, which is at the upper range of that of trabecular bone (2–12 MPa) [11]. However the scaffolds only nucleated apatite in SBF after 7 days' immersion, with the SBF being refreshed daily. This may be too low for a rapid bond to form in vivo. The foam replication process is also difficult to upscale for mass production, due to problems with removing excess glass slurry prior to sintering, in addition to the common problem of hollow centered struts that one would often find in this kind of scaffolds. The aim of this work was therefore to produce a porous scaffold with improved bioactivity using a processing method that can be up-scaled to the required ISO standards.

Gel-casting is a technique that has previously been used to produce dense or porous ceramic or metal structures. The process involves forming a gel by in situ polymerization of organic monomers [12–13]; in doing so the gel binds the particles and is burnt out during sintering of the particles. The process was adapted by Sepulveda et al. to produce porous hydroxyapatite (HA) foams by introducing a foaming step into the original process prior to gelation [14–17]. The HA foams had superior interconnected pore networks to those produced by more conventional methods, such as sacrificial space holder technique, and improved mechanical properties over those produced by sacrificial polymer foam templating.

The aim of this work is to produce an amorphous melt-derived bioactive glass porous scaffold with a suitable pore network for bone in-growth. The glass composition was designed to allow sintering but also have a bioactivity similar to the 45S5 composition, by keeping the network connectivity (mean number of bridging oxygen bonds per silicon atom) as close to 2 as possible [18]. Eq. (1) was derived by Ray et al. [19] to calculate network connectivity of the glass; however a modified version that takes into account the phosphorus forms $Q^0$ orthophosphate structures was used to calculate the network connectivity in this paper, An example of such calculation is displayed as Eq. (2) in the case of Bioglass®.

$$\mathrm{NC} = 2 + \frac{\text{Total No. of bridging oxygens} - \text{No. of nonbridging oxygens}}{\text{Total No. of possible bridges}} \quad (1)$$

$$\mathrm{NC} = 2 + \frac{2 \times \text{mol.\%}\,(\mathrm{SiO_2}) - 2 \times \text{mol.\%}\,(\mathrm{CaO} + \mathrm{Na_2O}) + 2 \times \text{mol.\%}\,(\mathrm{P_2O_5} \times 3)}{\text{mol.\%}\,\mathrm{SiO_2}} \quad (2)$$

The gel-cast foaming process was chosen because it has the potential to produce highly connected spherical pores and its ability of mass reproduction. The objectives were to adapt the gel-cast foaming process for use with glasses by investigating the processing variables and to produce a bioactive glass scaffold which has compressive strength similar to porous bone and an interconnected pore structure suitable for bone regeneration.

## 2. Materials and methods

### 2.1. Glass characterization

ICIE 16 (49.46% $SiO_2$, 36.27% CaO, 6.6% $Na_2O$, 1.07% $P_2O_5$ and 6.6% $K_2O$, in mol.%) was the chosen glass composition [18]. The relevant oxides were mixed together in their relative proportions and heated to 1420 °C, in a platinum crucible, and held for 1.5 h followed by quenching in water at room temperature. The coarse frit form of the glass was collected and dried overnight. The solid form of the glass was ground to a powder (Glen Creston Ltd. Gy-Ro Mill) and sieved at <38 μm (Endecotts EFL 2000/1).

Differential scanning calorimetry (DSC) (Stanton Redcroft DSC 1500, Polymer Laboratories, Loughborough, UK) using a ramp rate of 10 °C $min^{-1}$ to a final temperature of 950 °C, with matched platinum crucibles, was applied to study the differences in the glass transition temperatures and crystallization behaviour of ICIE 16 and Bioglass® (46.1% $SiO_2$, 26.9% CaO, 24.4% $Na_2O$, 2.6% $P_2O_5$, in mol.%). The modal particle sizes ($D_{50}$ value from laser scattering, CILAS 1064) of both glasses were 8 μm.

### 2.2. Verification of the gel-casting foaming process variables

Porous glass foams were produced by adapting the gel-cast foaming process. Fig. 1 shows the steps in the process and Table 1 details the reagents and their role in the procedure, based on the work by Sepulveda et al. [14–17,20].

Glass powder was mixed with deionized (18 Ω) water, the monomer (acrylamide) and the cross-linker (*N*,*N*'-methylene bisacrylamide) to produce a slurry. The dispersant (Dispex) was added to help further dispersion of glass powder in the solution. The mixture was then vigorously agitated to produce a foam with the aid of the surfactant (Triton X100). Polymerization was activated by the addition of the initiator (ammonium persulfate solution, concentration 0.52 g $ml^{-1}$) and the catalyst (tetramethylethylene diamine), which reacted with each other, releasing a free radical particle. This free radical then reacted with both the acrylamide and the *N*,*N*'-methylene bisacrylamide, forming a polymer network. Viscosity increased over a period of 1 min until gelation. Immediately (~2 or 3 s) prior to the gelation, the foam was cast into moulds. The pore structure was stabilized by the completion of gelation. It was then dried and sintered to burn out the organic matter, leaving the porous glass network.

Apart from the monomer (6 g), the cross-linker (3 g), the dispersant (2 drops) and the surfactant (0.1 ml), which were kept constant throughout, the influence of all other components on both the gelling time and the foam body was investigated systematically. Using a base protocol of 14 g glass, 20 ml water, 6 g mono-

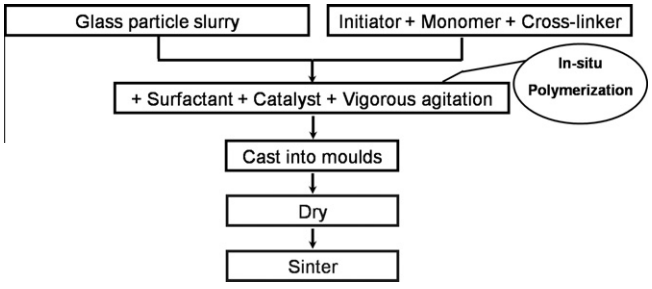


**Fig. 1.** Flow chart of the gel-cast foaming process.

**Table 1**
Gel-cast foaming process variables.

| Order | Components | Role |
|---|---|---|
| 1 | Glass powder (<38 μm) | |
| 2 | Ultra-purified water | Medium |
| 3 | Methacrylamide | Monomer |
| 4 | *N*,*N*'-methylene bisacrylamide | Cross-linker |
| 5 | Ammonium persulfate (APS) solution | Initiator |
| 6 | Dispex | Dispersant |
| 7 | Triton X100 | Surfactant |
| 8 | Tetramethylethylene diamine (TEMED) | Catalyst |