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Potassium based bioactive glass for bone tissue engineering

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Abstract

A fundamental issue for the restoration of bone defects according to a tissue engineering approach is the development of highly porous bioactive scaffolds. The polymer burning out method is widely employed to fabricate bioceramic scaffolds because of its versatility, simplicity and low cost. However, the resulting scaffolds may suffer low porosity and non-interconnected pores. In the present contribution a new fabrication method is presented. Thanks to a recently developed potassium-based bioactive glass, which has the peculiarity to be sintered at a relatively low temperature (i.e. ~750 °C), it was possible to use sodium chloride particles as pore generating agents, which helped to maintain the shape of the struts during the entire sintering process. The salt particles can be easily removed by immersing the scaffold in water, giving place to a structure that combines high porosity (in the 70–80 vol.% range) with interconnected pores and an appreciable mechanical behaviour (Young's modulus in the 3.4–3.7 MPa range according to compression tests).

Keywords: B. Porosity; D. Glass; D. Glass ceramics; E. Biomedical applications

1. Introduction

The development of bone tissue engineering [1,2] has drawn an increasing attention on scaffolds design. Scaffolds [3,4], which are among the key ingredients in the field of tissue engineering, are temporary 3D templates to improve osteoblast cells attachment and proliferation. The final goal is to obtain synthetic bone graft substitutes, which are of fundamental importance wherever it is required to treat skeletal defects caused by traumatic events or degenerative diseases associated with aging [5].

Ideal scaffolds should be highly bioactive and mimic the human bone morphology, which is highly porous with an interconnected pore network [6,7]. At the same time, adequate mechanical properties are required in order to match those of the host tissue.

In the last few years, scaffolds based on bioceramics, such as synthetic hydroxyapatite (HA), $Ca_{10}(PO_4)_6(OH)_2$ [8], or β-tricalcium phosphate (β-TCP) [9], have been extensively employed in dentistry and orthopedic applications, especially as coating materials for metallic implants [10–12]. Recently bioactive glasses, such as 45S5 Bioglass®, have been used for scaffolds design because of their high bioactivity index [13,14]. However, the relatively low strength of bioactive glasses and their brittleness require the employment of thermal treatments in order to improve their mechanical reliability. Usually, sintering processes are performed at temperatures between 900 and 1100 °C [15]. Bretcanu et al. have recently demonstrated that the optimal sintering temperature and time for 45S5 Bioglass® are 1050 °C and 140 min, respectively [16]. These temperatures are higher than the sodium chloride melting temperature, i.e. 801 °C [17], therefore 45S5 Bioglass® cannot be employed in the protocol subject of the present work. Recently, a new glass composition has been formulated by substituting the sodium oxide with the potassium oxide into the 45S5 Bioglass® composition [18]. The obtained glass, named BioK, is here employed for the first time to produce scaffolds for bone regeneration and repair. Compared to the 45S5 Bioglass®, the BioK can be sintered at lower temperatures, i.e. at 750 °C, obtaining compact samples. This peculiarity has made it possible to develop a new technique to realize scaffolds, which may represent an alternative to other conventional techniques, such as the burning out method [19]. Briefly, in the burning out method organic particles, used as pore generating

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agents, are added to the ceramic powders and subsequently burned out during sintering. The resulting samples may suffer low porosity values or non-interconnected pores [20,21]. This fact, on one side, may hinder the growth of bone tissue within the scaffolds, on the other side may cause poor vascularization, resulting in tissue inflammation and necrosis [22]. The inadequate porosity caused by blind pores can be due to the high difference between the sintering temperature of 45S5 Bioglass® and the melting point of the organic fillers employed as pore formers. For example, in a typical polyethylene burning out procedure, the 45S5 Bioglass® is thermally treated between 950 and 1050 °C [15], while the polyethylene melting point is between 110 and 130 °C [23]. This means that the organic pore formers are eliminated "too soon" from the system, i.e. when the structure is not sufficiently densified. For this reason, the glass powders may occlude the pores and their shape is no longer maintained. This issue can be overcome by using porogens which are able to remain within the scaffold during the sintering process. Thanks to the low sintering temperature of BioK, it was possible to use sodium chloride powders as porogens. Subsequently, once the heat treatment is finished and the scaffold is compact, the sodium chloride is removed by leaching.

2. Materials and methods

As previously mentioned, the formulation of BioK was derived from that of 45S5 Bioglass® substituting the Na_2O with K_2O [18]. The resulting BioK proportions are 46.1 mol% SiO_2, 26.9 mol% CaO, 24.4 mol% K_2O (which substituted Na_2O), 2.6 mol% P_2O_5. A detailed characterization of this glass was reported elsewhere [18]. Briefly, BioK particles were prepared by melting the raw powders materials (commercial reagent-grade SiO_2, $CaCO_3$, K_2CO_3 and $K_3PO_4{\cdot}H_2O$ by Carlo Erba Reagenti, Italy) in a platinum crucible at 1450 °C for 1 h and then by rapidly quenching in water. The obtained frit was then ball-milled and sieved to a final grain size below 38 μm.

The scaffolds were then prepared by mixing the BioK particles with a proper amount of sodium chloride powders sieved to a final grain size below 600 μm. Various amounts of sodium chloride were added to the BioK powders, in order to obtain the best compromise between porosity and compactness. In particular, the following glass-to-sodium chloride ratios were selected:

- BioK1: 40 vol.% of BioK powders and 60 vol.% of sodium chloride powders;
- BioK2: 30 vol.% of BioK powders and 70 vol.% of sodium chloride powders;
- BioK3: 27 vol.% of BioK powders and 73 vol.% of sodium chloride powders.

Sodium chloride contents below 40 vol.% were considered too low to produce an adequate porosity, while contents higher that 75 vol.% did not yield reproducible green compacts.

All compositions were mixed for 30 min in a polyethylene bottle using rolls shaker. Then, green bodies were produced by uniaxial pressing BioK1, BioK2 and BioK3 powders at 140 MPa for 10 s. Acetone was used as liquid binder. The pressed samples were heat-treated in a furnace in order to sinter the glass powders. The thermal treatment was performed at 750 °C for 3 h with a heating rate of 10 °C/min. The sodium chloride particles did not melt and hence preserved the original pore shape during the entire sintering process. At the end of the thermal treatment, the samples were removed from the furnace and cooled down to room temperature in air. Afterwards, the samples were briefly immersed in distilled water at 80 °C to remove the sodium chloride particles by leaching. The water was agitated by magnetic stirring and frequently replaced until a complete removal of sodium chloride was obtained. Finally, the scaffolds were dried overnight in a furnace at 110 °C.

The scaffolds microstructure was investigated by scanning electron microscope SEM (ESEM Quanta 2000, FEI Co., Eindhoven, The Netherlands).

The total porosity (vol.%) of the scaffolds was evaluated according to the following calculation:

$$P_{\%} = \left(1 - \frac{W_f}{W_0}\right) \times 100 \quad (1)$$

where $P_{\%}$ is the total pore content (vol.%), W_f is the measured weight of the scaffold and W_0 is the theoretical one obtained by multiplying the scaffold volume by the BioK density which was measured to be $\rho = 2.65$ g/cm^3 by means of a pycnometer test (Micromeritics AccuPyc 1330, Georgia, USA). In order to validate the porosity values, optical microscope images were considered and analyzed. In particular, for each kind of scaffold, at least five images were acquired with an optical microscope equipped with a 10× objective. The area occupied by the pores was quantified by means of image analysis (UTHSCSA Image Tool).

To qualitatively assess the scaffolds permeability, capillarity tests were performed. To this aim, a solution with a viscosity similar to that of the human blood was used.

The mechanical properties of the scaffolds were measured under compression test using a mechanical testing machine (MTS, QTest/10). Five porous samples (15 mm × 17 mm × 15 mm size) were evaluated for each composition. The samples were tested at room temperature. The cross-head speed was set at 0.01 mm s^{-1}.

3. Results and discussion

A photograph of a BioK1 sample, produced with the new processing protocol, was reported in Fig. 1(a), together with details of the external surface perpendicular (Fig. 1(b)) and parallel (Fig. 1(c)) to the pressing direction.

Fig. 2 shows some micrographs with details of the BioK1 surface and internal structure. In Fig. 2(a) and (b) it is possible to observe the presence of a widespread porosity with pores of different sizes, ranging from a few tens of microns to several hundreds of microns. The average pore size is greater than 100 μm, which is considered to be the minimum value required to allow bone cells infiltration and tissue in-growth