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Review

Composite bone cements loaded with a bioactive and ferrimagnetic glass-ceramic: Leaching, bioactivity and cytocompatibility

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ABSTRACT

In this work, composite bone cements, based on a commercial polymethylmethacrylate matrix (Palamed®) loaded with ferrimagnetic bioactive glass-ceramic particles (SC45), were produced and characterized in vitro. The ferrimagnetic bioactive glass-ceramic belongs to the system SiO_2–Na_2O–CaO–P_2O_5–FeO–Fe_2O_3 and contains magnetite (Fe_3O_4) crystals into a residual amorphous bioactive phase. Three different formulations (containing 10, 15 and 20 wt.% of glass-ceramic particles respectively) have been investigated. These materials are intended to be applied as bone fillers for the hyperthermic treatment of bone tumors. The morphological, compositional, calorimetric and mechanical properties of each formulation have been already discussed in a previous paper. The in vitro properties of the composite bone cements described in the present paper are related to iron ion leaching test (by graphite furnace atomic absorption spectrometer), bioactivity (i.e. the ability to stimulate the formation of a hydroxyapatite – HAp – layer on their surface after soaking in simulated body fluid SBF) and cytocompatibility toward human osteosarcoma cells (ATCC CRL-1427, Mg63). Morphological and chemical characterizations by scanning electron microscopy and energy dispersion spectrometry have been performed on the composite samples after each test.

The iron release was negligible and all the tested samples showed the growth of HAp on their surface after 28 days of immersion in a simulated body fluid (SBF). Cells showed good viability, morphology, adhesion, density and the ability to develop bridge-like structures on all investigated samples. A synergistic effect between bioactivity and cell mineralization was also evidenced.

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1. Introduction

The oncological hyperthermia is a therapy frequently used for the treatment of solid tumors. The treatment consists of the increase of the cancer wound temperature above the physiological values (>41–42 °C) by means of microwave or radiofrequency devices. The rationale behind this approach is that, above this temperature, the healthy cells are able to survive, while the cancer cells die for accidental (coagulative necrosis) or programmed cell death (apoptosis) [1]. Recent clinical studies have confirmed the efficacy of the hyperthermia to determine the cancer degeneration. Moreover, heat is able to enhance the efficacy of some chemotherapeutic agents with a synergic or additive effect. The hyperthermia can also favor the penetration of the drug in the tumor nodules by overworking the vasodilatation due to the thermal increase [2]. Actually, the prevalent clinical application of this therapy is the hyperthermic perfusion chemotherapy for the solid tumors (melanoma or sarcoma of the soft tissues). The major limit of this procedure is the need of repeating the treatments by means of invasive approaches, if a single treatment is not sufficient [3]. The heating of the tissues can also be performed by using implantable magnetic materials in the tumoral zone, which can be heated by the application of an alternating magnetic field. The alternating magnetic field has a poor interaction with the tissues and, on the contrary, it can heat the magnetic materials through well-known phenomena (hysteresis loss and induced eddy currents). If these materials are implanted in the organism, they can indirectly heat the nearby tissues [4]. Up to now, the magnetic materials used for this purpose are composite materials, which contain a magnetic phase dispersed in a biocompatible matrix (albumin, polymers, ceramic materials) [5,6]. The magnetic phase can be composed by metals (Fe), metal alloys (in the system Fe–Co–Ni), metal oxides (Fe_2O_3, Fe_3O_4), and ferrites ($LiFe_5O_8$, $MgFe_2O_4$), often in the form of nanoparticles [7,8]. The principal disadvantages are that, for their use, some of these materials (as the metal alloys) require the application of a very intense alternating field, difficult to realize in a hospital, and some of them are not always biocompatible. Furthermore all these materials are unlikely integrated in the tissues, since they are based on bio-inert formulations.

Recently, new approaches for the preparation of magnetic bone substitutes have been described, like bioactive (Fe^{2+}/Fe^{3+})-doped hydroxyapatite (Fe-HAp) with superparamagnetic-like properties [9] as well as hydroxyapatite-based scaffolds with magnetic properties obtained by dip-coating in aqueous ferrofluids containing iron oxide nanoparticles [10,11], with the aim of attracting and taking up *in vivo* growth factors, stem cells or other bio-agents bound to magnetic particles via magnetic driving, but they are not intended for hyperthermic treatment of bone tumors.

In the present work innovative magnetic biomaterials for the cancer treatment by not invasive hyperthermia have been synthesized and characterized by in vitro tests. The proposed materials are composite bone cements based on polymethylmethacrylate (PMMA, an acrylic resin used in the majority of cements and bone filler) loaded with glass-ceramic powders (named SC45), which have both bioactive and magnetic properties, characteristics that none of the materials reported in the above-mentioned literature possess at the same time. The amorphous phase of the glass-ceramic assures bioactivity properties, where bioactivity is intended as the ability to establish a chemical bond between the implant and the biological tissue. The presence of the magnetic phase guarantees the possibility of obtaining a localized heating of the tissue around the implant by means of hysteresis loss. The composite bone cements characterized in this work could be proposed for the treatment of both the primary and secondary bone tumors: they can be used as fillers of bone cavities, also of complex shape, having the ability of promoting a fast functional restart (due to their high osteointegration and osteoinduction potentialities) as well as the ability of producing heat, if subjected to an alternating magnetic field. The heating effect can be used to apply a hyperthermal therapy, killing the tumor cells not surgically removed or those formed during an eventual relapse. Among different commercial formulations, Palamed® was chosen as polymeric matrix for the present study, since it is one of the most commonly used PMMA-based bone cements. However, it is worth of mentioning that the addition of the bioactive and ferrimagnetic glass-ceramic (SC45 powders) can be extended to any other commercial or experimental formulation, taking into account the different component ratios and physical properties of other bone cements, because it does not imply any modification into the polymerization mechanism of the organic matrix. Any improvement or modification of the commercial polymeric phase it is foreseen by the addition of the glass-ceramic phase, and the present paper is only intended to investigate the role of the new inorganic additional phase (SC45) on the final properties of a common PMMA-based bone cement.

The composite bone cement object of the present paper have been already completely characterized in a previous work [12] in terms of morphological and compositional properties, heating properties (by calorimetric measurements) and mechanical properties (compression and bending tests). In brief, an optimal dispersion of SC45 powders in the PMMA matrix was achieved, the cements were able to generate heat in an alternate magnetic field, and the power loss increased with the increase of the applied magnetic field and with the amount of SC45 in the cement. Preliminary mechanical tests also showed both compression and flexural strength above the ISO requirement, at least for the formulations with the lowest amount of SC45.

In the present paper the attention is focused on the in vitro properties of the composite bone cements, both in terms of bioactivity (i.e. the ability of stimulate mineralization) in a simulated body fluid and cytocompatibility toward osteoblast-like cells.

2. Materials and methods

2.1. Production of the glass-ceramic and of the composite material

SC45 is a bioactive glass-ceramic belonging to the system SiO_2–CaO–Na_2O–P_2O_5–Fe_2O_3–FeO. This composition was developed and optimized by Bretcanu et al. in previous works [13–16]. The SiO_2–CaO–Na_2O–P_2O_5 oxides are mixed in the same ratio of the 45S5 bioactive glass (Bioglass®) [17] and the addition of iron oxides (Fe_2O_3 and FeO) was performed choosing their amounts in order to obtain a theoretical amount of magnetite of 45 wt.%. The chemical composition of the glass-ceramic is reported elsewhere [13–16].

As reported in [12,13], the reactants (Sigma Aldrich) were melted in a platinum crucible at 1550 °C in a high temperature furnace (Nabertherm-Carbolite 1800) for 25 min, using a heating rate of 10 °C/min. The melt was then cooled at room temperature in air and poured in a brass mold (obtaining bulk samples). The crystallization of magnetite occurred during cooling of the melt, obtaining glass-ceramic samples. The bulk was then milled in a planetary ball mill with zirconia jar (Vibratory Micro Mill PULVERISETTE 0 Fritsch) and sieved below 20 μm. This grain size was chosen during a previous work [12] since it assured poor agglomeration phenomena of the glass-ceramic powders and in turn, good handling and mixing properties with the polymeric matrix of the cement.