Bioactive Ferrimagnetic Glass-ceramics for Magnetic Induction Hyperthermia

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ABSTRACT

Ferrimagnetic glass-ceramics are potential candidates for magnetic induction hyperthermia [1]. The aim of this work is the preparation and characterization of innovative bioactive ferrimagnetic glass-ceramics in the system SiO_2–Na_2O–CaO–P_2O_5–FeO–Fe_2O_3. These biomaterials contain different amounts of nanometric or sub-micrometric magnetite crystals, homogeneously distributed in an amorphous matrix. They show bioactivity properties, making them also suitable for bone substitutions. The influence of the chemical composition and processing condition (temperature, time, atmosphere) on the glass-ceramics microstructure and on their properties has been analysed. The specific power loss of these biomaterials varies in the range 20-65 W/g, in function of the glass-ceramic microstructure. The surface of these materials can be easily modified, in order to bind specific proteins for magnetic drug targeting.

Keywords: bioactive, ferrimagnetic, glass-ceramic, hyperthermia, cancer.

1 INTRODUCTION

Magnetic induction hyperthermia is one of the therapies employed in cancer treatment. This method involves biocompatible magnetic materials, which generate heat under an alternating magnetic field. These biomaterials are implanted into a neoplastic tissue and the patient is placed in an extra-corporeal magnetic field. The magnetic materials will heat, due to various loss mechanisms, producing tissue necrosis or thermoablation. The heating temperature depends on the materials properties, magnetic field parameters (intensity, frequency) and tissue characteristics (blood flow, tissue density, type of tumoral cells, etc.) [2].

2 MATERIALS AND METHODS

The ferrimagnetic glass-ceramics synthesised in this work belong to the system SiO_2–Na_2O–CaO–P_2O_5–FeO–Fe_2O_3. They were realised by two different synthesis methods: melting of the starting materials and sintering of a mixture of bioactive glass and magnetite powders [3].

For the first method, the precursors were solid powders (oxides, carbonates or phosphates), which were mixed and then melted at temperatures in the range 1400–1550°C. The raw materials for the preparation of glass-ceramics can also be obtained by wet chemistry (coprecipitation) in order to achieve higher purity and better homogeneity. For the sintering process, composite materials have been prepared by mixing a bioactive glass powder with magnetite powder. The powder mixtures were pressed and then thermally treated at temperatures between 800–1000°C, in argon atmosphere.

Part of the glass-ceramic samples was milled and sieved under 45 μm diameter. Another part was cut into small pieces $5 \times 5 \times 2$ mm^3, polished with SiC paper and washed with distillate water in an ultrasonic cleaner.

X-ray diffraction (XRD) was employed for analysing the glass-ceramic microstructure (identification of the crystalline phases, determination of the crystallite size, lattice constant, lattice strain). The diffraction pattern was fit by using the Rietveld method.

Glass transition temperature and thermal stability were investigated by differential thermal analysis (DTA) and thermo-gravimetric analysis (TGA).

The morphology of the crystals was studied by scanning and transmission electron microscopy (SEM and TEM).

Magnetic hysteresis cycles were analysed using a vibrating sample magnetometer (VSM) with a maximum applied field of 12 kOe (956 kA/m), at room temperature, in quasi-static conditions. Calorimetric measurements were carried out using a magnetic induction furnace, with a magnetic field of 40 kA/m and a frequency of 440 kHz.

The bioactivity behaviour has been analysed by soaking the samples in a simulated body fluid (SBF) [4] at pH=7.42. The variation of the pH of the SBF solution, after soaking of the glass-ceramic samples, was measured twice a week, for a month. The specimens were periodically removed from the SBF and washed with distilled water. After drying in air atmosphere, the surface of the samples was observed by SEM in order to assess their bioactivity by detecting the formation of hydroxylapatite on their surfaces.

3 RESULTS

Different shapes of the glass-ceramic samples, before grinding and sieving, can be observed in Figure 1. SEM micrograph of a glass-ceramic sample after grinding and sieving is presented in Figure 2.

Figure 1 Different shapes of glass-ceramics

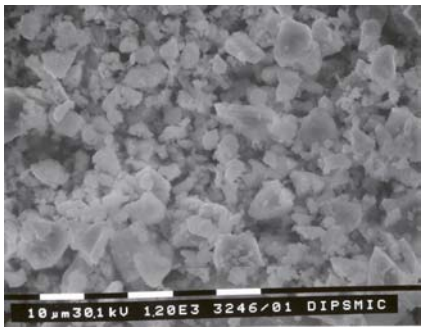

Figure 2 SEM micrograph of a glass-ceramic sample after grinding and sieving

3.1 X-ray diffraction

XRD patterns put in evidence the presence of a unique crystalline phase, magnetite, embedded in an amorphous residual phase. The XRD pattern of a glass-ceramic sample is shown in Figure 3. The (hkl) reflections of magnetite are pointed out on the graphic. The amorphous halo can be observed in the range $2\theta = 20–40°$.

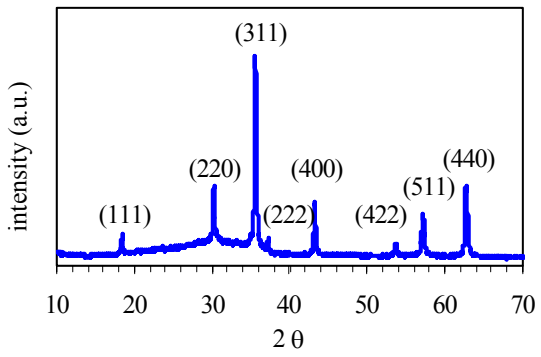

Figure 3 XRD pattern of a glass-ceramic sample

The microstructure depends on the materials composition and the process conditions (temperature, time, atmosphere). The magnetite crystals have nanometric or sub-micrometric dimensions and they are homogeneously distributed in the residual amorphous matrix. The quantity of magnetite in the samples varies from 20-45 wt. %, in function of the starting composition. The values of the unit-cell parameter (a_0) of the crystallised magnetite are close to the crystallographic reference data.

3.2 Thermal analyses

The thermal analyses of these samples reveal a specific behaviour of glass-ceramic materials. All samples present a glass transition temperature (Tg), confirming the presence of the residual amorphous phase in the glass-ceramic samples.

3.3 Scanning electron microscopy

The characteristic shape of the magnetite crystallised in the glass-ceramic samples is illustrated in Figure 4 (after chemical etching with 1:1 HNO_3:HF solution, 5% vol. in water). Straight interpenetrated columns containing small different size crystals can be observed. Each crystal has an octahedral shape, characteristic for a phase with a cubic structure, as magnetite. These small crystals with octahedral morphology are identified as an iron oxide by EDS analysis. As can be observed in this micrograph, the small columns are uniformly distributed in the amorphous matrix.

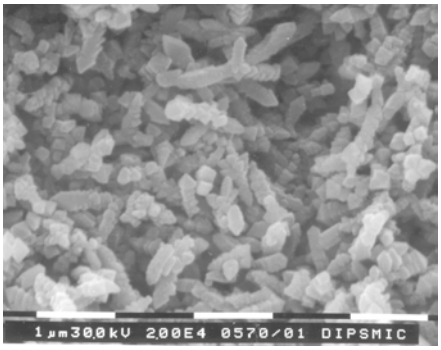

Figure 4 SEM micrograph of a glass-ceramic sample after chemical etching

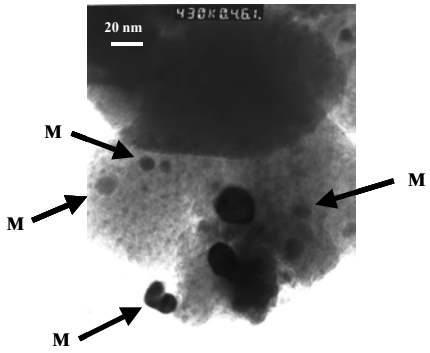

Figure 5 TEM micrograph of a glass-ceramic sample

3.4 Transmission electron microscopy

The TEM micrograph of a glass-ceramic sample is shown in Figure 5. Small dark grey particles (see arrows), embedded in the amorphous phase (light grey colour) can be seen. These particles present a large distribution in the range of 5-10 nm. They are identified as magnetite from electron diffraction pattern.

3.5 Magnetic measurements

The room temperature hysteresis loops for pure magnetite and glass-ceramic samples under a magnetic field of 10 kOe (796 kA/m) are shown in Figure 6. It can be seen that these materials exhibit similar magnetic behaviour, characteristic of soft magnetic materials, with narrow hysteresis cycle. On the right bottom of the Figure 6 is presented a zoom-in plot of the central part of the hysteresis loop, in order to emphasise the coercive field and the remanence magnetisation. The specific power loss of glass-ceramic samples, in function of the synthesis method, for an applied field of 40 kA/m and 440 kHz is represented in Figure 7. The values of the magnetic parameters are reported in Table 1. As can be observed, the specific power loss of the samples varies in the range 20-65 W/g, in function of the glass-ceramic microstructure.

The amount of magnetite in the samples affects in a significant way their magnetic properties. It has a great influence on glass-ceramic structure and therefore, on the hysteresis cycle parameters. The saturation magnetization increases with the content of magnetite in the glass-ceramic samples. Coercivity and remanence are strongly affected by the microstructure. Magnetic anisotropy, shape and dimension of the crystals, residual stress and crystal imperfections influence the coercive and remanent field.

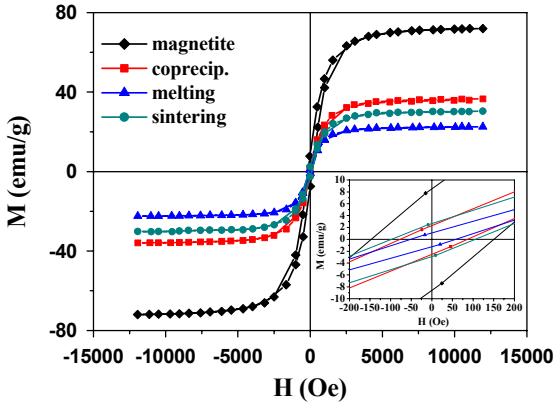

Figure 6 Room temperature hysteresis cycle

By soaking of 1 g of these samples into 20 ml of water, after two minutes of the application of the magnetic field (40 kA/m, 440 kHz), the water temperature increases in the range 20-100°C. The estimated values are reported on the last row of the Table 1.

Characteristics	Coprec.	Melting	Sint.
Crystals size (nm)	30-60	45-85	< 5000
Quantity of magnetite (wt %)	20-45	15-35	31-44
Saturation magnetisation (emu/g)	15-33	14-32	28-40
Coercitive force (Oe)	80-220	35-180	55-105
Remanence magnetisation (emu/g)	2-6	1-8	1-5
Maximum field saturation (kOe)	1-5	3-5	5-6
Interpolated hysteresis area ± 500 Oe (erg/g)	1700-3900	900-5200	1200-4300
Specific Power loss (W/g)	25-65	20-60	26-56
ΔT (°C/g)	36-93	27-87	37-80

Table 1 Crystals size and magnetic parameters

The maximum increasing of the temperature in function of the synthesis method, under an alternating magnetic field of 40 kA/m and 440 kHz, is plotted in Figure 8.

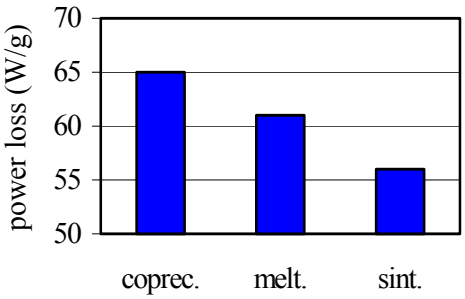

Figure 7 Variation of the specific power loss in function of the synthesis method, for an applied field of 40 kA/m and 440 kHz.

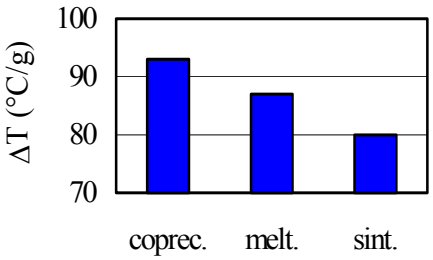

Figure 8 The increasing of the temperature produced by 1 g of glass-ceramic samples, immersed in 20 ml distillate water, after 2 minutes of the application of the magnetic field (40 kA/m; 440 kHz)

3.6 Bioactivity test

All the samples show bioactivity properties, as after few days of immersion in a simulated body solution, hydroxylapatite crystals precipitate on their surface. SEM micrograph of the surface of a glass-ceramic after soaking in SBF for 14 days is presented in Figure 9. The globular shape of the crystal aggregates, characteristic of precipitated hydroxylapatite, can be clearly seen. The hydroxylapatite is formed on the top of the silica-rich gel layer, whose characteristic structure (full of cracks, due to the drying process) can be observed.

EDS analyses show the presence of Ca and P ions, with the atomic ratio Ca/P close to the one of hydroxylapatite (1.67). Moreover, hydroxylapatite was identified by XRD analysis. Therefore, after soaking for 14 days in SBF, a homogeneous layer of precipitated hydroxylapatite is formed.

Figure 9 SEM micrograph of the surface of a glass-ceramic sample after soaking in SBF for 14 days

4 DISCUSSION

Melting of high purity wet-chemistry derived precursors gave the best results from the point of view of heat generation and presents fast bioactivity kinetics. Unfortunately, this synthesis method uses expensive raw materials and the process parameters need a severe control. Anyway, when both bioactive and magnetic properties are required, this method could be efficiently utilised.

Melting of commercial reagent grade raw materials shows good results regarding specific power loss but has the slowest bioactivity kinetics. This method is easily to apply and could be successfully used when slow reaction kinetics is needed.

The best results for the bioactivity kinetics were obtained with the sintering method. This method is easier to reproduce and could be used when bioactivity properties are predominant.

Due to the bioactivity behaviour, these glass-ceramics could be also used for bone substitutions. After surgical resection, these materials could form a chemical bond with bone, improving the bone regeneration ability.

5 CONCLUSIONS

Ferrimagnetic glass-ceramics with the composition in the system SiO_2–Na_2O–CaO–P_2O_5–FeO–Fe_2O_3 have been prepared by different methods. The microstructure and the magnetic properties have been optimised in function of the chemical composition and the process conditions (row materials, temperature, time, atmosphere). The selection of the synthesis method could be made in function of the tissue characteristics and magnetic field conditions. Therefore, the heat generation of the glass-ceramic samples can be tailored in function of materials properties. Thus, it is possible to choose the appropriate material that reveals the best compromise among those properties, which are the most relevant to the clinical application. Moreover, as other glasses and glass-ceramics, the surface of these materials can be easily functionalised, in order to bind specific proteins for magnetic drug targeting.

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