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Magnetic glass ceramics for sustained 5-fluorouracil delivery: Characterization and evaluation of drug release kinetics

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ABSTRACT

In the present study, magnetic glass ceramics in the system $Fe_2O_3 \cdot TiO_2 \cdot P_2O_5 \cdot SiO_2 \cdot MO$ (M = Mg, Ca, Mn, Cu, Zn or Ce) are prepared. The effect of adding different cations on the thermal behavior, developed phases, microstructure and magnetic properties is studied using differental thermal analysis (DTA), X-ray diffraction analysis (XRD), transmission electron microscope (TEM), FT-infrared transmission (FT-IR) and vibrating sample magnetometer (VSM) respectively. The magnetic glass ceramics are tested as delivery systems for 5-fluorouracil. Modeling and analysis of release kinetics are addressed. The application of Higuchi square root of time model and the first order release model indicated that, 5-FU is released by diffusion controlled mechanisms, and that its released rate depends greatly on the concentration of loaded drug during the loading stage. The obtained results suggested that, the prepared magnetic glass ceramics can be used for cancer treatment by hyperthermia and/or by localized delivery of therapeutic doses of 5-fluorouracil.

1. Introduction

Magnetic nanoparticles showed great potential applications in magnetic fluids, catalysis, biotechnology, biomedicine, magnetic resonance imaging (MRI), magnetic recording devices, and environmental remediation [1,2]. Recently magnetite (Fe_3O_4) received more attention due to its potential applications in nano biotechnology. It was used as a tag for sensing and imaging, as well as an active agent for antitumor therapy [3–5]. For high performance in specific biological applications, magnetic nanoparticles (Fe_3O_4) should be spherical, biocompatible, super paramagnetic, have narrow size distributions, moderate size, high crystallinity, large surface areas (for maximal protein or enzyme binding), high magnetic saturation to provide maximum signal, and good dispersion in liquid media [1].

Many substantial progress were made to control the size of magnetic nanoparticles as co-precipitation [6], thermal decomposition [7,8] and hydrothermal synthesis [9]. However, these methods showed some disadvantage. They are: 1) polydispartion by co-precipitation method; 2) additional treatments are needed to convert the hydrophobic magnetite nanoparticles, prepared by organic routs, to the hydrophilic ones, which are more suitable for biomedical applications [10,11]; 3) the prepared nanoparticles have low magnetization per particle, and hence, it is difficult to effectively separate them from the solution or control their movement in the blood by using moderate magnetic fields and 4) the use of expensive organic agents and high temperature leading to large wastage of materials and energy. Therefore, it is necessary to find out an economical and more efficient process for a large-scale production of mono-disperse water soluble Fe_3O_4 nanoparticles with high saturation magnetization (SM) to meet the requirements for biomedical applications. Glass ceramic materials seem to have the properties which meet these requirements.

Glass-ceramics are defined as composite materials containing at least one crystalline phase dispersed in an amorphous glassy matrix, so magnetic glass-ceramics can be viewed as composites materials containing dispersed magnetic particles in a glass matrix. These materials are important for developing compact glass ceramics and glass coated magnetic particles, with applications in material science [12–19] and biotechnology [20–22]. Recently, glass coated magnetic nanoparticles are investigated, for delivering drugs to specific body locations in new health treatment procedures [23–26]. More recently, obtaining glass-ceramic containing high contents of magnetic nanoparticles with well-controlled particle size attracted a considerable interest from the material science community. The chemical composition of the glass precursor influences the physical and chemical properties of the formed magnetic nanoparticles in the glass ceramics. Therefore, the investigation of new glass ceramic materials containing magnetic nanoparticles with controlled particle size distribution and aspect ratio is quite desirable.

The wide objective of our work is preparation and characterization of compact bodies from glass ceramics. The prepared glass ceramic is composed of behavior maintained single domain magnetic particles (<100 nm) and glass matrix in which magnetic nanoparticles are well dispersed. It is carried out through studying the sequence of crystallization in the system $Fe_2O_3 \cdot TiO_2 \cdot P_2O_5 \cdot SiO_2 \cdot MO$ (M = Mg, Ca, Mn, Cu, Zn

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or Ce). The particles are separated by a nonmagnetic matrix that lowers the sintering temperature, prevents the particles from growing to multi-domain ones and leads to low magnetic interaction between magnetic nanoparticles, which make them suitable for localized anticancer drug delivery. The prepared magnetic glass ceramics are designed to have dual jobs, i.e. killing cancer cells by hyperthermia and/or delivering therapeutic doses of anticancer drug at the infected site, which prevents cancer cells from local recurrence and/or their metastatic spread to other parts of body. The produced glass ceramics are characterized using DSC, XRD, TEM, and VSM techniques. In addition, they are tested as delivery systems for 5-fluorouracil.

2. Experimental methods

2.1. Preparation of the glass

Chemical compositions of samples under investigation in mole % are given in Table 1. The compositions are designed to indicate the effect of adding different cations on the sequence of crystallization in the system $Fe_2O_3 \cdot TiO_2 \cdot P_2O_5 \cdot SiO_2$. Samples are denoted according to the added cation as GMg, GCa, GMn, GCu, GZn and GCe. As our target is to obtain glass-ceramics so a melting step is necessary to achieve the nucleation process in the liquid-derived amorphous phase. 100 g of each composition is well mixed in a ball mill for 15 min, and then the batches are melted in a Pt crucible in an electrically heated furnace at 1200–1450 °C for 2 h. Occasional swirling every 30 min is carried out to ensure homogenization. The melt of each sample is poured onto a stainless steel plate at room temperature. The poured sample is pressed into a plate of 1–2 mm thickness by another cold steel plate.

2.2. Crystallization of the glasses

The thermal behavior of the finely powdered glass samples is examined using SETRAM Instrumentation Reulation, Labsys™ TG-DSC16 under inert gas. The powdered glasses are heated in Pt-holder with another Pt-holder containing Al_2O_3 as a reference material. The obtained results are used as a guide for determining the required heat-treatment temperatures, which are needed to induce further crystallization in the samples.

2.3. Characterization

Samples before and after heat treatments, are subjected to powder X-ray diffraction (XRD), using Ni-filter and Cu-K_α target, to identify the precipitated crystalline phases. XRD was performed using Bruker D8 Advanced Instrument (Germany D8 ADVANCE Cu target 1.54 Å, 40 kv, 40 mA). The reference data for the interpretation of the X-ray diffraction patterns were obtained from ASTM X-ray diffraction card files.

The heat-treated samples were crushed and sonically suspended in ethanol, few drops of the suspended solution were placed on an amorphous carbon film held by a copper microgrid mesh, and then they were examined using JEM 2010 transmission electron microscope to study the microstructure and crystallite size.

Table 1
Chemical composition of the glass ceramics samples in mol%.

Sample	mol%									
	Fe_2O_3	TiO_2	P_2O_5	SiO_2	MgO	CaO	MnO_2	CuO	ZnO	CeO_2
GMg	40	5	15	20	20	–	–	–	–	–
GCa	40	5	15	20	–	20	–	–	–	–
GMn	40	5	15	20	–	–	20	–	–	–
GCu	40	5	15	20	–	–	–	20	–	–
GZn	40	5	15	20	–	–	–	–	20	–
GCe	40	5	15	20	–	–	–	–	–	20

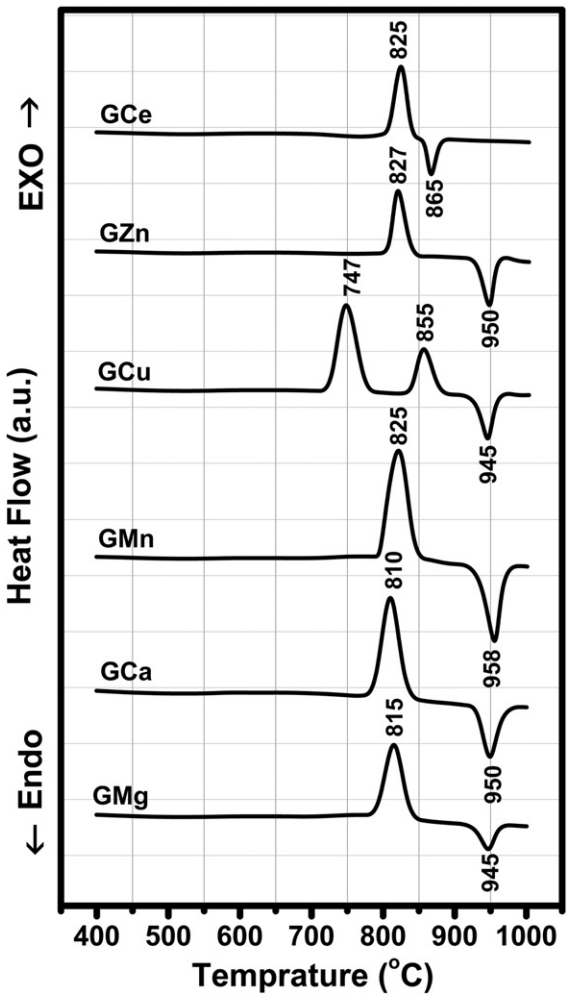

Fig. 1. DTA analysis of quenched samples.

The magnetic properties of the as prepared and heat treated samples were measured at room temperature, using a vibrating sample magnetometer (VSM; 9600-1 LDJ, USA), in a maximum applied field of 20 kOe. From the obtained hysteresis loops, the saturation magnetization (Ms), remanence magnetization (Mr) and coercivity (Hc) were determined.

The FT infrared absorption spectra were measured at room temperature in the wavenumber range of 400–4000 cm^{-1} by a Fourier-transform infrared spectrophotometer (type 5000, Mattson, USA). The glasses were pulverized into fine powder, and then 2 mg of the fine glass powder was mixed with 200 mg KBr powder. The mixture was subjected to a load of 5 ton/cm^2, in an evocable die for 2 min, to produce homogenous transparent disks. The FTIR measurements were carried out immediately after preparing the disks.

Surface area of the samples was measured with a high-speed gas sorption analyzer (NOVA 2000 series, Chromatic, UK) at 77 K.

2.4. Loading of 5-fluorouracil (5-FU) onto samples

The loading experiments were carried out in tris buffer solution. The pH is adjusted to 7.4. 5-Fluorouracil was dissolved in tris buffer solution by rapid mixing in a vortex apparatus, for 5–10 min. Drug concentrations of 1000 mg/L and 3000 mg/L were used in this experiment. 0.3 g of each sample was immersed in 5 ml of drug solution containing 1000 mg/L and another 0.3 g of the same sample was immersed in drug solution containing 3000 mg/L of the drug