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Lanthanide-doped $Y_3Ga_5O_{12}$ garnets for nanoheating and nanothermometry in the first biological window

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ABSTRACT

Absorption and luminescence spectra in the first biological window of Nd^{3+} single-doped and Er^{3+}-Yb^{3+} co-doped $Y_3Ga_5O_{12}$ nano-garnets have been studied to evaluate their potential use as simultaneous optical nano-heaters and nanothermometers in biomedicine. Nd^{3+}-doped nano-garnets uses the 808 nm laser radiation, resonant with the largest absorption peak of the $^4I_{9/2} \rightarrow {}^4F_{5/2}$ transition, for both heating the nanoparticle and populating the $^4F_{3/2}$ emitting level. Changes in the relative intensities of different emission peaks between Stark levels of the $^4F_{3/2}$ ($R_{1,2}$)→$^4I_{9/2}$ ($Z_{1\text{-}5}$) transition can be directly related to the temperature of the nano-garnet. On the other hand, the Yb^{3+}/Er^{3+} combination takes advantage of the large absorption cross-section of the Yb^{3+} ions at around 920 nm to heat the sample, while triggering the Yb^{3+}-to-Er^{3+} upconversion energy transfer processes that populate the thermally coupled $^2H_{11/2}$,$^4S_{3/2}$ emitting levels of Er^{3+} ions, whose relative intensity changes with temperature can be calibrated. Accurate spatially- and temperature-controlled optically stimulated heating of these nano-garnets from room temperature up to 75 °C within the first biological windows is proved.

1. Introduction

Efficient luminescent nanostructures allowing, with a single laser beam, simultaneous optically-activated temperature sensing and heating, as well as imaging, for *in vivo* thermal treatments of subtissue tumors has been a hot topic in biomedicine in the last years [1]. Metallic nanoparticles, quantum dots, carbon nanostructures, porous silicon, organic nanoparticles and lanthanide-doped nanocrystals have been extensively studied for photothermal therapies [1–3]. The hyperthermia treatment, in which the cancer cells are heated to the cytotoxic level (43–45 °C), needs a careful and accurate thermal sensing for *real-time* control of the absorbing energy of the laser radiation, minimizing the collateral damage that could arise from excessive heating [1–7].

The first difficulty arises from the optical radiation that should be used, since the ultraviolet and the high energy part of the visible light cannot penetrate efficiently into human tissues because of the combination of light scattering, due to tissue inhomogeneities, and light absorption, caused by different compounds present in real tissues, such as hemoglobin and water [8]. In order to overcome this limitation, the luminescent nanoparticles used in biophotonic applications should be excited and should emit in the biological windows (BWs) of the human tissues, i.e. in those energy ranges in which the tissue is more transparent to optical radiation, assuring greater penetration and lower damage [9]. The first biological window (1-BW) ranges from ~650 to ~970 nm, in which the absorption of water and other compounds, such as hemoglobin, are relatively weak. The 2-BW, located entirely in the near-infrared (NIR) range, extends from ~1000 to ~1400 nm, limited by two strong absorption bands of water, whereas the 3-BW extends from ~1500 to ~1700 nm also in the NIR range. For example, carbon nanotubes have been used for *in vivo* imaging using the 1-BW [10] and lanthanide-doped nanoparticles have been used for *real-time* infrared *in vivo* imaging within the 2-BW [11].

Conventional infrared thermometry based on the black body radiation only provides accurate temperature at the skin's surface. Nowadays, the emergence of nanotechnology has opened new lines of research for the use of the luminescent nanoparticles for subtissue thermal sensing [9,12–14]. Nanothermometry is especially important in

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biomedicine and can help extracting knowledge of the local dynamics and performance of the majority of biological microorganism (cell, bacteria, …) that are strongly determined by temperature, and whose sizes are larger than the nanoparticles. Optical nanothermometers are calibrated using different techniques (changes in lifetime, polarization, bandwidth, etc.), although the most widely used is that in which the relative intensities of the emissions from two closed-energy, thermalized levels is related to temperature [15–19]. The luminescences of quantum dots, colloidal and lanthanide (Pr^{3+}, Nd^{3+}, Er^{3+} or Tm^{3+}) doped nanocrystals have been calibrated as local temperature probes [12–14,20]. Moreover, in biomedicine applications the strategies for improving the temperature detection at the nanometer scale in the first biological window has involved the synthesis of sophisticated core-shell nanoarchitectures in combination with non-linear upconversion processes using different lanthanide ions [21,22].

After laser excitation, heat is induced by the generation of phonon modes in the vibrating nanostructure, whose energy is subsequently transferred to the surrounding medium. The thermal sensitivity plays an important role in the careful control of the spatial location and heat transfer rate to the cell, which is directly related to the nanometer size of the particle and its large surface-to-volume ratio. Garnet nanostructures show good biologic compatibility and relatively small cytotoxicity, compared to quantum dots, and they do not need functionalization to enter in the cells. In addition, they show high transparency from the UV to the mid-IR range, good chemical stability, high thermal conductivity, and high energy phonons to generate heat [20,23].

For the design and synthesis of multifunctional nanoparticles capable of simultaneous heating and thermal sensing, doping with lanthanide trivalent ions has the advantage of having multiple absorption and emission bands in the BWs, with multiple combinations of NIR excitations and NIR detections [1]. The first attempt to optically stimulate heating was done by Bednarkiewicz *et al.* [4] using Nd^{3+}-doped $NaYF_4$ nanoparticles and, more recently, Nd^{3+}-doped LaF_3 nanoparticles have been used for simultaneous thermal therapy, as nanoheater and nanothermometer, and *in vivo* imaging using the 1- and 2-BWs [7].

In this work we analyze the absorption and luminescence properties of Nd^{3+} single-doped and Yb^{3+}/Er^{3+} co-doped lanthanides in $Y_3Ga_5O_{12}$ nano-garnets as simultaneous heaters and thermometers in the wavelength range of the 1-BW from ~780 to ~920 nm, and in the biological temperature range, from room temperature up to 70 °C.

2. Synthesis and experimental techniques

Nanocrystalline yttrium gallium garnets of composition $Y_{3(1-x)}Ln_{3x}Ga_5O_{12}$ (YGG), with x = 0.01, and 0.10 and Ln = Nd, Er, and Yb, were synthesized by the citrate sol-gel method in air [20,23–25]. These moderate doping concentrations have allowed making a proof-of-concept for the real ability of using the YGG nanogarnets as optically-controlled multifunctional nanoparticles for simultaneous heating and thermal sensing purposes, using laser excitation and spontaneous photon emission within the 1-BW, although higher concentrations of lanthanide ions (Nd^{3+} and Yb^{3+} in this work) are expected to benefit the light-to-heat conversion [4,6].

The powder was obtained as agglomerated nanocrystals with different shapes and sizes ranging from 40 to 60 nm (see Fig. 1) [23,24]. In addition, they show low cytotoxicity, at least with concentrations up to 120 μg/mL, and do not need any functionalization to enter the cell [26]. X-ray powder diffraction (XRPD) patterns were measured on a diffractometer PANalytical X'Pert Pro using $CuK_{\alpha 1}$ radiation. The fitted XRPD pattern for YGG is shown in Fig. 1. All the reflections are well indexed to a single cubic phase with space group *Ia*-3d (No. 230, Z = 8), where no impurity phase has been detected. The corresponding unit cell parameters have been obtained by fitting the profiles of the nanogarnets by the Rietveld method [27] using FullProf program [28]. According to the reliability factors (χ^2 = 8.8; R_p = 12.8; R_{wp} = 11.7; R_{exp} = 3.94), quite goodness of fitting parameters has been reached. The garnet structure can be described as a network of GaO_6 octahedra and GaO_4 tetrahedra linked by shared oxygen ions at the corners. The polyhedra are arranged in chains along the three crystallographic axes and form dodecahedral holes, with D_2 local point symmetry, which are occupied by the Y^{3+} and Ln^{3+} ions. The structural, vibrational and optical properties of these nano-garnets are quite similar to those of the bulk garnet crystal [20,23–25].

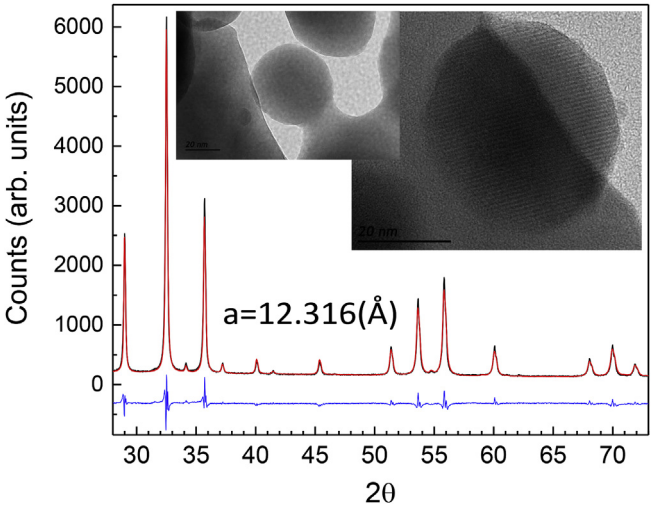

Fig. 1. X-ray diffraction pattern of YGG nano-garnets (black). Rietveld refinements including the differences (blue) between calculated (red) and observed (black) patterns are also shown. HRTEM micrograph (20 nm scale) of YGG nano-garnets. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Diffuse reflectance spectra of the powder samples have been measured with a spectrophotometer (Agilent Cary 5000) equipped with an integrating sphere. The Stokes and upconverted emission spectra were measured with a 0.3 m focal length spectrograph (Andor Shamrock 303i) equipped with a Peltier cooled silicon CCD camera (Andor Newton) by exciting the lanthanides with a tunable cw Ti: sapphire laser (Spectra Physics 3900 S) pumped by a 532 nm diode laser (Spectra Physics Millenia Prime Laser 15s JSPG). For temperature calibration, nanoparticles were located at the center of a tubular furnace (± 0.7 °C resolution) and measurements were taken following a 180° configuration [17–19]. During laser heating, a period of 2 min where taken to achieve the steady-state temperature regime before measuring. All spectra were corrected from instrument response.

3. Results

The optical properties of the lanthanide ions depend on the local structure of these ions in the nano-garnets, since it rules the fine structure splitting of the $^{2S+1}L_J$ multiplets and the intra-configurational *4f-4f* electric-dipole transitions probabilities [29]. Lanthanide ions will occupy the 8-coordinated orthorhombically distorted D_2 dodecahedral sites replacing the Y^{3+} ions without charge compensation, which completely breaks the free-Nd^{3+}, -Er^{3+} and -Yb^{3+} ions degeneracies and giving rise to (2 J + 1)/2 Stark, or crystal-field, levels [20,23–25] (see Fig. 2).

The studies of the Nd^{3+} and Yb^{3+}/Er^{3+} in the YGG nano-garnets as simultaneous heaters and thermometers in the 780–920 nm NIR range of the 1-BW have followed two main steps: firstly, an accurate optical calibration of the temperature using the fluorescence intensity ratio (FIR) technique [9,17–19]; and secondly, the correlation between the laser pump density and the local temperature of the area irradiated by the laser [4,7].