Synthesis and characterization of Na(Gd_{0.5}Lu_{0.5})F₄: Nd³⁺, a core-shell free multifunctional contrast agent

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Abstract

Compared to conventional core-shell structures, core-shell free nanoparticles with multiple functionalities offer several advantages such as minimal synthetic complexity and low production cost. In this paper, we present the synthesis and characterization of Nd³⁺ doped Na(Gd_{0.5}Lu_{0.5})F₄ as a core-shell free nanoparticle system with three functionalities. Nanocrystals with 20 nm diameter, high crystallinity and a narrow particle size distributions were synthesized by the solvothermal method and characterized by various analytical techniques to understand their phase and morphology. Fluorescence characteristics under near infrared (NIR) excitation at 808nm as well as X-ray excitation were studied to explore their potential in NIR optical and X-ray imaging. At 1.0 mol% Nd concentration, we observed a quantum yield of 25% at 1064 nm emission with 13 W/cm² excitation power density which is sufficiently enough for imaging applications. Under 130 kVp (5mA) power of X-ray excitation, Nd³⁺ doped Na(Gd_{0.5}Lu_{0.5})F₄ shows the characteristic emission bands of Gd³⁺ and Nd³⁺ with the strongest emission peak at 1064nm due to Nd³⁺. Furthermore, magnetization measurements show that the nanocrystals are paramagnetic in nature with a calculated magnetic moment per particle of ~ 570 μ B at 2T. These

preliminary results support the suitability of the present nanophosphor as a multimodal contrast agent with three imaging features viz. optical, magnetic and X-ray.

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1. Introduction

Rare earth doped materials find several potential applications in several areas such as lasers, optical temperature sensors, white light-emitting diodes, and dye-sensitized solar cells [1-6]. With the introduction of nanotechnology there are so much interest in the development and applications of rare earth based multifunctional nanomaterials. One of the most important areas is biomedical imaging, where nanomaterials with multiple imaging features have been used as contrast agents.[7-9] Several imaging modalities, such as X-ray/ computed tomography (CT), magnetic resonance imaging (MRI), and optical imaging, currently use contrast agents to improve cell and tissue images. The variation of each imaging modality offers a unique advantage in spatial resolution, imaging depth, sensitivity, and ease of use.

Several multimodal inorganic contrast agents with core-shell structures have been reported in the past. For example, core-shell quantum dots (QD) have been proposed as a suitable multimodal agent due to their unique optical properties such as multiplexing capabilities, photostability, and high fluorescence yield.[10-14] Coupling the QDs with the magnetic metal ion core can lead to a dual model contrast agent. However, there are several significant shortcomings

1 with these imaging agents. QDs show several undesirable properties such as luminescence
2 blinking, high toxicity, and requiring precise size tuning.[15,16] Core-shell upconverting
3 nanoparticles have been shown to be a viable multimodal imaging agent since they are excited in
4 the near infrared (NIR) region and yield emission in the visible region with comparatively better
5 signal-to-noise ratio, low photodamage, and better penetration depth.[17] With the inclusion of
6 Gd^{3+} and Fe^{3+} ions in the overall core structure, multimodal imaging features can be
7 achieved.[18-20] An un-doped outer shell has even been shown to enhance the multimodal
8 features of the core material.[19] But, one of the major issues with core-shell structured
9 nanoparticle is the synthesis complexity and the associated cost of production.

10 In order to circumvent these difficulties, a core-shell free structure was proposed where
11 multiple functionalities can be easily achieved by doping metals with the desired properties into
12 the same lattice. This can be easily accomplished in wide band gap materials such as oxides,
13 halides, chalcogenides, etc. For example, trivalent rare earth metals are considered to be suitable
14 dopants for narrow band tunable emission with a very wide range of excitation and emission in
15 the UV-VIS-IR range.[22] Unlike QDs and organic dyes, these phosphors are free from
16 photobleaching and do not need size control for color tunability. In addition, they have a long
17 decay time and excellent IR absorbing features that enables imaging in the upconversion and
18 downconversion mode. By replacing a fraction of the metal cations in the lattice with another
19 cation having magnetic properties, a luminomagnetic nanostructures can be easily accomplished
20 without the need of a core-shell structure. To date, several researchers have developed
21 luminomagnetic nanocrystals (NCs) as potential multimodal imaging agents with core-shell free
22 nanostructures.[23-27]

This paper discusses the synthesis and characterization of core-shell free $\text{Na}(\text{Gd}_{0.5}\text{Lu}_{0.5})\text{F}_4:\text{Nd}^{3+}$ (NGL) as a potential NIR sensitive luminomagnetic nanophosphor for multimodal imaging application with three functionalities viz. NIR emission, X-ray fluorescence, and magnetic properties. NGL belongs to the NaYF_4 structure and is a wide band gap halide with an optical band gap of near 8 eV.[28] The multimodal properties of these NCs is achieved by utilizing the strong NIR fluorescence properties of the rare earth Nd^{3+} , magnetic properties of Gd^{3+} , and the high X-ray absorption properties of Gd^{3+} and Lu^{3+} in the NGL host. To the best of our knowledge, this is the first study reporting the synthesis and characterization of fully monodispersed water-soluble core-shell free nanophosphors with three imaging features.

2. Materials and Methods

2.1 Synthesis

The nanocrystals were synthesized via solvothermal (ST) method using 99.9% purity precursor chemicals (GFS Chemicals, US). To make Nd^{3+} doped $\text{Na}(\text{Gd}_{0.5}\text{Lu}_{0.5})\text{F}_4$ (NGL), stoichiometric amounts of $\text{L}(\text{NO}_3)_3$ ($\text{L}=\text{Gd}, \text{Lu}, \text{Nd}$) and 1g of the surfactant polyvinylpyrrolidone (PVP) were dissolved in 30 ml of ethylene glycol (Reagent, GFS Chemicals, US). The solution was then mixed with 0.21 g of sodium fluoride and 0.5 g ammonium fluoride in 20 ml of ethylene glycol. The resulting solution was heated to 200°C for 24 hours in an 80 ml stainless steel autoclave. After the reaction was completed, the nanoparticles were precipitated by adding excess ethanol and separated by centrifuging at 10,000 rpm (Z323, Labnet, U.S.) and subsequently washed 6 times with ethanol. Finally, the particles were freeze dried (25EL Freezmobile, VirTis, US) for 15 hours to obtain the powder.

2.2 Phase and Morphology

The X-ray powder diffraction (XRD) measurements were done with an automated diffractometer (Ultima IV, Rigaku, Japan) with Cu K α ($\lambda = 1.5$ Å) using Ni-filtered Cu K α radiation at 44 keV and 30 mA. The data was collected in the 20° to 60° range using a step size of 0.05° and a count time of 0.15 second. The particle size and morphology of the NCs were characterized by using a high resolution transmission electron microscope (HRTEM, JEOL ARM 200F) operated at 200 keV along with selected area diffraction (SAED) was used to determine the crystallinity of the samples. Electron dispersive x-ray (EDX) spectrum was obtained using a probe size of 0.13 nm and probe current 86 pA. Digital micrograph software GATAN was used for the image analyze.

2.3 Spectroscopic Characterization

Optical absorption spectrum of the powder was obtained using a spectrophotometer in the scattering mode (Perkin Elmer Lambda 19, US.). Fluorescence characterization of the synthesized particles were done by exciting the sample with a near infrared (NIR) 808 nm power tunable 14-Pin butterfly module laser diode (Axcel Photonics, B2-808-3000-150) that was controlled by a laser diode driver (Throlabs LM74S2 Driver, Thorlabs Laser Diode Control LDC2000-2A) and the emission from the sample was collected by the spectrofluorimeter (Quanta Master 51, Photon Technology International Inc., US) with an InGAS detector (Teledyne Judson Technologies, 062-8451, US). Photoluminescence decay curves were measured on a Quanta Master 40 system (Photon Technology International Inc., US) using the single shot transient digitizer technique with a nitrogen laser pumped dye laser (PTI part GL-3300 + GL-302) as excitation source. The nitrogen laser has an 800 ps pulse width that pumps a high resolution dye chamber to give 525 ± 0.04 nm light. The collected decay curve was analyzed using built in software provided by PTI. For the quantum yield (QY) measurements, a barium

sulfate coated integrating sphere (203 mm in diameter) (Oriel, Model 70451) was used and is mounted on the side of the spectrofluorimeter sample chamber, opposite to the excitation source. Powder sample was held in a specially designed sample holder with a quartz window to hold the powder in place and mounted at the sample port of the integrating sphere. The diffuse fluorescence spectra from the sample and the laser profile were recorded with the spectrofluorimeter by exciting the sample with an 808 nm power tunable fiber coupled Fabry Perot laser diode (Axcel Photonics, B2-808-3000-150). Fluorescence output from the sphere was collected via a liquid light guide (LLG) with a specially designed baffle that prevents the direct entry of the exciting laser beam into the detector. The LLG collects the light from the sphere and feeds to the InGAS detector through the emission monochromator. More details regarding the QY can be seen in our previous publications.[29, 30]

2.4 Magnetic Characterization

Magnetic properties of the samples were measured using a Superconducting Quantum Interference Device (SQUID) in the Magnet and Low Temperature Facility, at Northwestern University. The hysteresis loop of magnetization at room temperature was recorded with the magnetic field sweeping from -5 to 5 Tesla. The sample weighed was determined to be 67 mg.

2.5 X-ray excited emission

To characterize the X-ray induced luminescence or X-ray-excited scintillation (XES), the samples were irradiated in a Faxitron X-ray Cabinet System (Model RX-650). The X-ray induced luminescence was collected in a coaxial transmission irradiation configuration with the sample centered under the X-ray source. Samples were made by pressing 10 mg of the synthesized powder materials using a 7 mm diameter mold in a hand-pellet press with consistent

pressure. Pellet samples were then mounted on a piece of angled teflon using double sided tape and placed ~2 mm in front of an optical fiber in the Faxitron system. The emitted light was collected with an optical fiber attached to the Edinburgh Instruments FLS920 spectrometer. All samples were excited over an X-ray range of 20 to 130 kVp (5 mA).

3. Results and Discussions

The crystalline phase of NGL was studied using the obtained XRD pattern shown in Figure 1. The peaks were indexed with the α -NaGdF₄ (PDF 027-0697) and β -NaGdF₄ (PDF 027-0699) phases. This mixed phase was seen in all dopant concentrations and the compositions of these two phases are estimated to ~ 88% α -NaGdF₄ phase (cubic) and ~ 12% β -NaGdF₄ phase (hexagonal). The mixed phase in the system is most likely due to the precursor ratio of Na-Gd/Lu in the host crystal where the phase and size can be effected.[31] We determined that the NGL cubic phase is within the Fm-3m (225) space group with the cell parameters a=b=c= 5.5180 Å.

A Transmission Electron Microscope (TEM) image of the 1 mol% Nd³⁺ doped NGL is shown in Figure 2(a), which reveal a quasi-spherical shape with an average size of 21.78±2.24 nm (Figure. 2(c)). The SAED pattern and lattice fringes in the HRTEM image of NGL are shown in Figure 2(b,d) which illustrates the high crystallinity of the nanoparticles. A line scan histogram of Figure 2(d) is shown in the inset of Figure 2(d) where the lattice spacing of NGL is about 0.318 nm which corresponds to the (111) plane of α -NaGdF₄. The EDX was performed on NGL (Figure 2(e)) where the mapping verified that the elements Gd, Lu, Na, and F were present in

Figure 1. X-ray diffraction of NGL with the XRD cubic reference data α -NaGdF₄ (PDF 027-0697) and β -NaGdF₄ (PDF 027-0699). The ratio between the two phases was calculated to be $\sim 88\%$ and $\sim 12\%$ respectively.

Figure 2. (a) TEM image of the $\text{Na}(\text{Gd}_{0.5}\text{Lu}_{0.5})\text{F}_4:\text{Nd}^{3+}$, (b) the SAED pattern, (c) Particle size distribution (d) HRTEM of NGL with inset shows a line profile with a lattice spacing of 0.318 nm which corresponds to the (111) plane of α -NaGdF₄, (e) EDX line scan mapping of the nanoparticle indicating the presence of elements F, Na, Gd, Lu.

the nanoparticle whereas 1 mol% of Nd is below the EDX threshold to be detected. Using the EDX data, the percentage of each element was estimated to be ~24% of F, ~21% of Na, ~28% of Gd, ~27% of Lu.

The optical absorption spectrum of 2 mol% of Nd doped NGL is shown in Figure 3(a) with spectral band notations for all observed transitions. The spectrum was obtained by converting the reflectance spectrum to absorbance by applying the Kubelka-Munk model.[32] The absorption spectrum shows all characteristics bands of Nd^{3+} with 574 and 794 nm as the two strongest bands (specifically the $^2\text{G}_{7/2}$ and the $^4\text{F}_{5/2} + ^2\text{H}_{9/2}$). To explore the NIR fluorescence spectral properties as a function of Nd^{3+} concentration, the samples were excited with an 808 nm diode laser under identical experimental conditions with a laser power density of 12.74 W cm^{-2} and the emission spectra was collected in the 850-1900 nm range (Figure 3(b)). The emission spectra shows four emission bands centered at 880, 1064, 1330 and 1800 nm which originate from the $^4\text{F}_{3/2}$ to $^4\text{I}_{9/2}$, $^4\text{I}_{11/2}$, $^4\text{I}_{13/2}$ and $^4\text{I}_{15/2}$ respectively. As usual, the band at 1064 nm shows the greatest intensity followed by the band at 880 nm. The fluorescence branching ratios of the emission bands are respectively 37.91% for the 880 nm band, 44.80% for the 1064 nm band, 12.05% for the 1330 nm band, and 5.24% for the 1800 nm band. Furthermore, all emission bands show the characteristic Stark splitting indicating high crystallinity of the sample. Concentration dependent emission data shows that the emission is strongest in 1 mol% of Nd doped NGL.

To determine the quantum yield (QY) of the NGL, an integrating sphere was calibrated with a material of known efficiency, and identical measurements were done following the standard reported procedure.[29,30] The QY was measured for different Nd concentrations and the results are plotted in Figure 3(c). The QY of NGL with the Nd dopant concentration of 0.1, 0.5, 1.0, 2.0 mol% were measured to be 5.40, 5.86, 25.36, and 16.54 % respectively with a power

Figure 3. (a) Absorption spectra of Na(Gd_{0.5}Lu_{0.5})F₄:Nd³⁺, (b) Emission spectra of Na(Gd_{0.5}Lu_{0.5})F₄:Nd³⁺ as a function of Nd concentration (0.1, 0.5, 1.0, 2.0 mol%) (c) Quantum yield of different emission bands as a function of Nd³⁺ concentration at a power density of 12.74 W/cm². (d) Decay curves of 1064 nm emission for various Nd concentrations.

density of 12.74 W cm⁻² under 808 nm excitation. Each individual emission band quantum yield was also measured and is shown in Figure 3(c). The 1064 nm emission line showed the highest overall quantum yield, followed by the 880 nm band. Comparatively, the QY of our NGL particles is higher than the value of 22% obtained by Chen et.al in 3 mol% Nd doped NaGdF₄. [21]

The fluorescence decay curves of the 1064 nm emission as a function of Nd³⁺ concentration is shown in Figure 3(d). All decay curves are found to be double exponential in nature and the decay time was obtained by the expression:

$$I(t) = A_1 \exp\left(-\frac{t}{\tau_1}\right) + A_2 \exp\left(-\frac{t}{\tau_2}\right)$$

1 where A_1 and A_2 are the fitting parameters and τ_1 and τ_2 are the fluorescence decay times. The
2 average decay time was obtained using the expression [33]

$$\tau_{av} = \frac{(A_1 \tau_1^2 + A_2 \tau_2^2)}{(A_1 \tau_1 + A_2 \tau_2)}$$

4 Using the above expression the average decay time obtained for 0.1, 0.5, 1.0 and 2.0 mol% Nd^{3+}
5 concentrations are respectively 247, 571, 511, and 330 μs . At 0.1 mol% Nd concentration the
6 decay signal was not so strong to get a reliable decay time. However, from 0.5 mol% Nd
7 concentration onward decay signal was strong enough to get reliable measurements. As usual, at
8 higher dopant concentration the decay time shows a decreasing tendency due to the energy
9 transfer between the Nd ions. [33] Longer decay times are desirable in time-gated fluorescence
10 bioimaging where longer lifetimes can be more discernable against the noise from scattered light
11 and autofluorescence.[34]

12 The room temperature magnetization curve of NGL is shown in Figure 4. By fitting the
13 magnetization curve with the Langevin function, the magnetic moment per particle for NGL was
14 found to be $\sim 570 \mu\text{B}$. [35] Considering the fact that these NCs contain 50% of Lu^{3+} and Gd^{3+} , this
15 value is comparable to that reported for similar NCs with 100% of either component, such as
16 NaGdF_4 . [20, 36]

17 Figure 5(a,b) shows the X-ray excited luminescence spectrum of NGL with 1.0 mol% Nd^{3+}
18 concentration. The spectrum shows a total of 10 emission bands corresponding to various
19 transitions in Gd^{3+} and Nd^{3+} as indicated. All of the emission bands are identified using the

Figure 4. Magnetization curve of $\text{Na}(\text{Gd}_{0.5}\text{Lu}_{0.5})\text{F}_4:\text{Nd}^{3+}$ at room temperature.

trivalent energy states of Gd^{3+} and Nd^{3+} and the emission mechanism is interpreted in the energy level diagram shown in Figure 5(c). Gd^{3+} shows a single emission line at 311 nm corresponding to the transition ${}^6\text{P}_{7/2} \rightarrow {}^8\text{S}_{7/2}$ while the remaining emission bands originate from various excitation states of Nd^{3+} . The emission intensity transitions under X-ray excitation is noticeably weaker compared to the NIR excitation at 808 nm which can be attributed to the high energy excitation of the NCs where the non-radiative losses are higher at various excited levels due to the thermalization of the 4f shell electrons with the conduction band levels. Furthermore, low X-ray excitation power density also contributes to the observed weaker emission whereas both Gd^{3+} and Lu^{3+} have high X-ray attenuation coefficients and can transfer the absorbed X-ray energy to lower lying energy levels of Nd^{3+} to enable the X-ray excited fluorescence in NGL.

4. Conclusions

We have synthesized Nd^{3+} doped $\text{Na}(\text{Gd}_{0.5}\text{Lu}_{0.5})\text{F}_4$ nanophosphor in 20nm size range. The crystal lattice was properly designed to incorporate multiple functionalities such as strong NIR emission, X-ray excited emission, and magnetic properties where the magnetic moment per

Figure 5. X-ray Emission spectrum of $Na(Gd_{0.5}Lu_{0.5})F_4:Nd^{3+}$ in the a) visible and, b) NIR region at 130 kvP X-ray excitation. c) Energy level diagram interpretation of the X-ray excited luminescence spectrum of $Na(Gd_{0.5}Lu_{0.5})F_4:Nd^{3+}$.

particle for NGL was found to be $\sim 570 \mu B$. The NC shows very strong NIR emission at 1064 nm with a quantum yield of $\sim 25.36\%$ under an 808 nm excitation at a power density of $12.74 W/cm^2$, which is sufficiently large enough for NIR imaging applications. Under X-ray excitation, the NCs show emission from Gd^{3+} and Nd^{3+} indicating the suitability of the present nanomaterial as an X-ray contrast agent.

1 In addition, the magnetic properties of the material enable them to be useful in magnetic
2 resonance imaging. Since the three functionalities are incorporated into a single nanoparticle
3 without the need for core-shell structure, synthesis complexities are avoided and the efficiency of
4 each of these functionalities can be controlled for by selecting the proper dopants as well as
5 concentrations. It is anticipated that such a multifunctional material could provide several
6 opportunities for future medical imaging applications. In conclusion, we successfully made a
7 nanoparticle system that possess three functionalities and our preliminary observations show the
8 potential application of these material as tri-modal imaging agents and further proof of concept
9 experiments are underway to show their multimodal imaging applications.

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Graphical Abstract

The multimodal nanocrystal, $\text{Na}(\text{Gd}_{0.5}\text{Lu}_{0.5})\text{F}_4:\text{Nd}^{3+}$, has the potential to improve future applications due to the inherent properties included in the crystal lattice such as NIR-NIR optical properties, magnetic properties, and X-Ray absorption and emission properties.