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Green synthesis of highly dispersed ytterbium and thulium co-doped sodium yttrium fluoride microphosphors for *in situ* light upconversion from near-infrared to blue in animals



Yuan Pu^{a,b}, Lifeng Lin^a, Dan Wang^{a,b,*}, Jie-Xin Wang^{a,c}, Jun Qian^d, Jian-Feng Chen^{a,b,c}

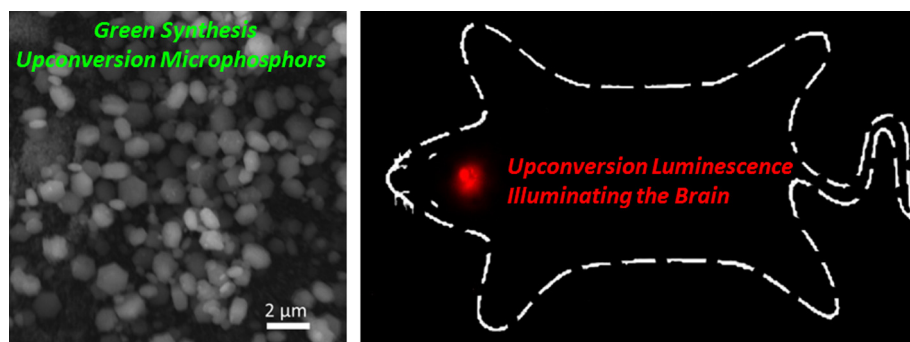
^a State Key Laboratory of Organic-Inorganic Composites, Beijing University of Chemical Technology, Beijing 100029, China

^b Research Centre of the Ministry of Education for High Gravity Engineering and Technology, Beijing University of Chemical Technology, Beijing 100029, China

^c Beijing Advanced Innovation Center for Soft Matter Science and Engineering, Beijing University of Chemical Technology, Beijing 100029, China

^d State Key Laboratory of Modern Optical Instrumentation, Centre for Optical and Electromagnetic Research, Zhejiang Provincial Key Laboratory for Sensing Technologies, Zhejiang University, 310058 Hangzhou, China

GRAPHICAL ABSTRACT



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ABSTRACT

We report a simple, low cost and environmentally friendly method to prepare $\text{NaYF}_4:\text{Yb}^{3+}, \text{Tm}^{3+}$ upconversion microphosphors (UCMPs) by thermal decomposition of rare earth-trifluoroacetate precursors using paraffin as the high boiling non-coordinating solvent. The UCMPs exhibited cubic phase with defined shape and bright upconversion luminescence. After coating with amphiphilic polymers of phospholipid-polyethylene glycol, the $\text{NaYF}_4:\text{Yb}^{3+}, \text{Tm}^{3+}$ UCMPs were highly dispersed in aqueous solutions and exhibited low cytotoxicity. Furthermore, we explored the use of the micro-injected micro-sized $\text{NaYF}_4:\text{Yb}^{3+}, \text{Tm}^{3+}$ particles for converting of near infrared into blue light in mice brain. The *in vivo* macroscopic upconversion luminescence imaging results showed that UCMPs located at 1 mm depth in the brain could be clearly distinguished. Microscopic upconversion luminescence imaging of the brain sections *in vitro* revealed that the UCMPs embedded at the particular location in brain tissues of mice were stable without significant diffusion in two weeks.

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1. Introduction

Rare-earth doped upconversion phosphors, which convert low energy near-infrared (NIR) light into high-energy ultraviolet or vis-

* Corresponding author at: State Key Laboratory of Organic-Inorganic Composites, Beijing University of Chemical Technology, Beijing 100029, China.

E-mail address: wangdan@mail.buct.edu.cn (D. Wang).

ible light, have recently attracted increasing attention in bio-related applications [1–3]. In comparison with traditional luminescent materials, such as organic dyes [4,5] and quantum dots (QDs) [6–8], the emission of upconversion phosphors were generated by excitation of continuous wave NIR laser, which was beneficial for enhancement the penetration depth and minimizing the autofluorescence of biological tissues [9–11]. Therefore, rare-earth doped upconversion nanophosphors (UCNPs) have been widely utilized to light-up the cells in deep tissues for fluorescence diagnosis [12–14], photodynamic therapy [15], and optogenetics [16]. However, the low upconversion efficiency of UCNPs is still far from perfect for such applications, particularly for optogenetics manipulations, which have an excitation light threshold for activation [17]. For photoactivation applications such as fluorescence diagnosis and photodynamic therapy, the phosphors are usually given by intravenous injection and should be small enough for long-time circulation in animals. In comparison, for optogenetics applications, the phosphors are expected to be embedded at a particular location in the neuronal plasma membrane, where the neurons are controlled by the exogenous expression of light-sensitive ion channels. Hence, when using upconversion phosphors for optogenetic applications, the phosphors should be designed with high upconversion efficiency for photoactivation and suitable sizes to avoid their diffusion in tissues. Comparing with rare earth doped UCNPs, upconversion microphosphors (UCMPs), which are much larger in size, usually present stronger upconversion emission due to their smaller surface-to-volume ratio and less surface quenching centers [18], promising for applications in optogenetic studies. Although powders of UCMPs are commercially available and used in for the visualization of IR radiation and security inks, they cannot be well suspended in aqueous or organic solutions to form colloidal dispersions, which limit their extending applications [19]. Thus, it is still valuable to explore facile methods for synthesis of highly dispersed UCMPs [20].

Upconversion phosphors are typically composed of an inorganic host lattice and rare-earth dopant ions embedded in the host lattice. Sodium yttrium fluoride (NaYF_4) has been widely used as a host in upconversion luminescence process due to its appropriate lattice matching with sensitizing ion (Yb^{3+}) and activating ions (Er^{3+} , Tm^{3+} , Ho^{3+}) high efficient upconversion phosphors [21]. Thus far, many approaches have been developed to synthesis rare-earth doped NaYF_4 upconversion phosphors with high quality, low cost and minimal toxicity [22–24]. The majority of these methods are substantially based on the thermal decomposition of rare earth-trifluoroacetate precursors in high boiling noncoordinating solvents (e.g., octadecene [25], trioctylphosphine [26]) or liquid precipitation reaction between soluble rare-earth salts and alkali fluorides. Along with others, we have reported the synthesis of lanthanide-doped rare-earth fluorides UCNPs by using eco-friendly paraffin liquid, instead of 1-octadecene, as the high boiling noncoordinating solvent [27,28]. However, as far as we are aware, the synthesis of $\text{NaYF}_4:\text{Yb}^{3+}$, Tm^{3+} microphosphors has been rarely reported.

In this paper, we report a green route for the synthesis of highly dispersed $\text{NaYF}_4:\text{Yb}^{3+}$, Tm^{3+} UCMPs by thermal decomposition of rare earth-trifluoroacetate precursors at 320 °C under ambient air pressure without inert gas protection. The paraffin liquid was employed as the high boiling noncoordinating solvent for the reactions and citric acid was used as the surface active agent. Both paraffin liquid and citric acid are natural products, with no toxicity and no environmental pollution [29], which are beneficial for wide-scale preparation of UCMPs. The UCMPs were then coated with amphiphilic polymers to form hydrophilic hybrid composites, abbreviated UCMPs@PEG. The morphology, structure and upconversion luminescence property of the UCMPs and UCMPs@PEG were investigated by scanning electronic microscope (SEM), trans-

mission electron microscope (TEM), powder X-ray diffraction (XRD), Fourier transform infrared (FTIR) spectrophotometry, thermogravimetric analysis (TGA) and luminescence spectra measurements. The cytotoxicity of UCMPs@PEG was determined by *in vitro* cell studies. Furthermore, the UCMPs@PEG particles were microinjected into the brain of mice. Macroscopic upconversion luminescence imaging of mice *in vivo* were carried out to investigate the abilities of the UCMPs@PEG for *in situ* light upconversion from near-infrared to blue in mice. Microscopic upconversion luminescence imaging of the brain sections *in vitro* were performed to study the long-term distribution of UCMPs@PEG in brain tissues of mice.

2. Experimental

2.1. Materials and instruments

Lanthanide oxides (Y_2O_3 , Yb_2O_3 , Tm_2O_3), trifluoroacetic acid, sodium fluoride, oleic acid, paraffin, chloroform, ethanol, and methanol were purchased from the Sigma Aldrich. 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-5000] (PEG) was purchased from Creative PEGWorks, Inc. Cell-culture products were purchased from Gibco. All the chemicals were used without any additional purification unless otherwise mentioned. Deionized water prepared by a Hitech Laboratory Water Purification System DW100 (Shanghai Hitech Instruments Co., Ltd) was used for all experiments.

The morphology studies were performed using a JEOL JSM-6360LV scanning electron microscope (SEM) and a Hitachi HT-7700 transmission electron microscope (TEM). The average size of the particles was calculated by measuring 100 particles from SEM and TEM images. X-ray powder diffraction (XRD) was carried out on a Japan Rigaku D/max rA X-ray diffractometer equipped with a $\text{Cu K}\alpha$ radiation. Dynamic light scattering (DLS) and zeta potential measurements were conducted by using a Malvern Zetasizer Nano ZS90 instrument. Triplicate samples were measured three times each at room temperature. The measurements were initiated within 3 min after sample preparation. Fourier transform infrared (FTIR) spectra were collected using a PerkinElmer spectrum GX FTIR system. A TA Instrument with a heating rate of 10 °C was used for the thermogravimetric analysis (TGA). Luminescence spectra of the NaYF_4 microphosphors was measured with a PG2000 spectrometer (Ideo Optics Instruments, China), using a 980 nm laser as the excitation light. *In vivo* luminescence imaging of mice was performed on a Maestro *in vivo* optical imaging system (CRI, Inc. Woburn, MA) equipped with a commercial 980 nm laser. Luminescence imaging of the brain slices of mice were acquired using an Olympus FV1000 laser confocal microscope equipped with a 980 nm laser.

2.2. Synthesis of $\text{NaYF}_4:\text{Yb}^{3+}$, Tm^{3+} upconversion microphosphors

In a typical synthesis approach of $\text{NaYF}_4:\text{Yb}^{3+}$, Tm^{3+} UCMPs, 0.025 mmol Tm_2O_3 , 0.25 mmol Yb_2O_3 , and 0.975 mmol Y_2O_3 were added to 20 mL of 50 % concentrated trifluoroacetic acid in a 250 mL flask. The mixture solution was heated to 80 °C to form a homogeneous solution and then slowly evaporated to remove water and excess trifluoroacetic acid, forming muddy mixture of $\text{RE}(\text{CF}_3\text{COO})_3$ ($\text{RE} = \text{Y}$, Yb , and Tm). Subsequently, 4.5 mmol NaF, 10 mL oleic acid and 30 mL paraffin liquid were added to the flask under vigorous stirring conditions and the mixture solution was slowly heated to 140 °C under vacuum for 20 min to remove water. The resulting solution with a slight yellow color was then heated to 320 °C at a rate of 10 °C/min in air and was kept at 320 °C for 1 h. Finally, the mixture was cooled to room temperature and precipi-

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