**Room Temperature Synthesis of Water-dispersible $\text{Ln}^{3+}:\text{CeF}_3$ ($\text{Ln} = \text{Nd}, \text{Tb}$)
Nanoparticles as Bimodal Probes for Fluorescence and CT Imaging.**

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ABSTRACT

The singular properties of lanthanide-based inorganic nanoparticles (NPs) has raised the attention of the scientific community in biotechnological applications. In particular, those systems with two or more functionalities are especially interesting. In this work, an effective and commercially attractive procedure has been developed that renders uniform, water-dispersible $\text{Ln}^{3+}:\text{CeF}_3$ ($\text{Ln}=\text{Tb}, \text{Nd}$) NPs with different shapes and size. The method consists of the homogeneous precipitation, in a mixture of polyol and water, of cations and anions using precursors that allow the controlled release of the latter. The advantages of the reported method are related to the absence of surfactants, dispersing agents or corrosive precursors as well as to the room temperature of the process. The obtained $\text{Tb}:\text{CeF}_3$ NPs produce an intense emission after excitation through the Ce-Tb energy transfer band located in the UV spectral region, thus being potentially useful as phosphors for *in-vitro* imaging purposes. On the other hand, the synthesized $\text{Nd}:\text{CeF}_3$ NPs are good candidates for *in-vivo* imaging because their excitation and emission wavelengths lie in the biological windows. Finally, the excellent X-ray attenuation efficacy of the $\text{Nd}:\text{CeF}_3$ NPs is shown, which confers double functionality to this material as both luminescence bioprobe and contrast agent for X-ray computed-tomography.

Keywords: lanthanide nanoparticles, Neodymium, fluorides, fluorescence, computed tomography

1. Introduction

Lanthanide-based inorganic nanoparticles (Ln-NPs), owing to their photostability and relatively sharp luminescence emission bands, are an excellent choice for potential use as phosphors in biotechnology, including biosensing,^[1] and luminescent bioimaging.^[2] In addition to luminescent bioimaging, certain Ln-NPs, mainly those based on Gd, Ho and Dy, have been proposed as contrast agents for magnetic resonance imaging (MRI) due to the paramagnetic nature of most lanthanide ions.^[3] Finally, because of the high atomic number (Z) of lanthanides, Ln-NPs have also been studied for potential use as contrast agents in X-ray computed tomography (CT).^[4] Among the different Ln salts, Ln fluorides are preferred as phosphors matrices because of the low phonon energy of the fluoride lattice ($<400\text{ cm}^{-1}$), which minimizes the non-radiative relaxation of the Ln excited states, therefore providing improved quantum efficiency to the phosphor.⁵⁶ Cerium fluoride (CeF_3), in particular, benefits from the well-known Ce^{3+} capacity to absorb ultraviolet (UV) radiation and efficiently transfer it to several active lanthanide ions like Tb^{3+} . Likewise, CeF_3 shows an extremely low solubility in water ($K_{\text{sp}} = 1.69 \cdot 10^{-20}$),^[7] which would make it non-toxic.^[8]

The synthesis of monodisperse particles in the nanometer scale is of key importance for their use in biotechnology.^[9] Particle size has especial influence on important processes involved in their *in vivo* applications such as their biodistribution, cell uptake, and excretion pathways and the optimum size is considered to be in the nanometer size range.^{[10][11]} To date, different approaches have been developed for the synthesis of Ln: CeF_3 NPs, including hydrothermal synthesis, microemulsion, sonochemistry, precipitation in highly boiling point solvents, etc. Most of these methods produce either aggregated NPs, as inferred from their TEM micrographs^[12,13,14,15,16] or large particles in the micrometer scale.^[17,18,19] Very few procedures yield, however, highly uniform and well dispersed Ln: CeF_3 particles with dimensions $< 100\text{ nm}$. Gai et al.,^[20] for example, reported the synthesis of highly uniform, monodisperse (15 nm) $\text{Tb}:\text{CeF}_3$ NPs by thermolysis of rare earth oleate complexes in a mixture of octadecene and oleic acid at 280°C . Following the polyol method and using polyethyleneimine (PEI) as a capping agent to control the particles growth, Li et al.^[21] obtained well dispersed $\text{Tb}:\text{CeF}_3$ nanorods at 200°C and nanocubes at 240°C , with a mean diameter of 10 nm. Although both methods produced well dispersed CeF_3 NPs, they suffer from drawbacks including high temperature synthesis and use of additives. In addition, the nanoparticles obtained

in the presence of oleic acid were hydrophobic and needed a second step in the synthesis process to make them hydrophilic and compatible with physiological fluids. Room temperature synthesis of nearly monodisperse, 20 nm Tb:CeF₃ NPs has been recently reported by Shcherbakov et al.^[8] by precipitation in isopropylalcohol from CeCl₃ and HF, with the shortcoming, however, associated to the use of hydrofluoric acid. Therefore, developing an effective, commercially attractive procedure working at mild or low temperatures, in the absence of surfactants, dispersing agents or corrosive precursors, to obtain uniform, water dispersible Ln:CeF₃ NPs is still a challenge.

Herein, we describe a facile method to synthesize uniform, water dispersible CeF₃ NPs in a mixture of water and polyol at room temperature. The size and shape of the NPs can be easily modified by changing the polyol type, used as solvent, while keeping all other parameters fixed. The uniformity and size distribution of the obtained NPs is assessed, not only from the corresponding TEM micrographs, but also from dynamic light scattering (DLS) data recorded on aqueous colloidal suspensions of the NPs, which give evidence of the absence of particle aggregation in the colloid.^[22] The microstructure and crystal structure of the different types of NPs synthesized are characterized by both XRD and high resolution TEM, including a tomography analysis to appreciate the 3D morphology of the particles. The method reported here is shown to be successful as well to obtain Tb³⁺- and Nd³⁺-doped CeF₃ NPs with the same morphological features as the undoped particles. Tb³⁺-doped CeF₃ NPs are good candidates as phosphors for *in-vitro* bioimaging purposes, given the intense emission produced through energy transfer from Ce³⁺ to Tb³⁺ after excitation in the UV spectral region. However, the limited penetration depth of visible light into biological tissues together with the harmful effects of UV radiation constitute serious difficulties for the use of these phosphors when facing *in vivo* imaging. In order to make the CeF₃ NPs useful for the latter purpose, Nd³⁺ ion has been selected as the optically active ion. This lanthanide ion is of particular interest in biotechnology because its excitation and emission wavelengths lie in the so-called biological windows, which ensures a minimal light attenuation and a minimal risk for the patient.^[23,24] The luminescence of both Tb³⁺- and Nd³⁺-doped CeF₃ NPs has been evaluated from both a static and a dynamic perspective to find the optimum doping level in each case. Finally, the ability of the Nd:CeF₃ NPs to absorb X-rays and their potential application as contrast agents in X-ray computed tomography has been evaluated and compared to that of a clinically used contrast agent.

2. Materials and Methods

2.1. Synthesis of samples

CeF₃ fluoride nanoparticles were obtained according to the following method: cerium nitrate (Ce(NO₃)₃·6H₂O, Sigma Aldrich, 99%) and sodium tetrafluoroborate (NaBF₄, Sigma Aldrich, 98%) were dissolved separately in 3 mL of an ethylene glycol/water (EG/H₂O) mixture (90/10 V/V) with magnetic stirring at room temperature. Both solutions were admixed together and aged at room temperature for 20 hours in glass tubes. The concentrations of Ce³⁺ and F⁻ in the final solution were 0.05 M and 0.72 M, respectively. The resulting suspension was centrifuged to remove the supernatants and washed, twice with ethanol and once with double distilled water. For some analyses, the powders were dried at room temperature. The reaction yield was approximately 60%.

Different Ce³⁺ and F⁻ sources as well as different concentrations of such cations were used to analyze their effect on the resulting particles characteristics. The Ce³⁺ sources were cerium acetate (Ce(CH₃COO)₃ · xH₂O, Sigma Aldrich, 99,99%) and cerium chloride (CeCl₃ · 7H₂O, Sigma Aldrich, 99,9%), while fluoride acid (HF, VWR, 40%), 1-butyl-2-methylimidazolium tetrafluoroborate (BMIMBF₄, C₈H₁₅BF₄N₂, Sigma Aldrich, 97%) and ammonium fluoride (NH₄F, Sigma Aldrich, 98%) were used as the fluoride sources. We also used solvents other than ethylene glycol, such as 1,3-butanediol (Fluka, 99.5%) and diethylene glycol (Sigma, 99.5%) as well as different polyol/water ratios to analyze the effect of the solvent nature on the particles morphology.

The Nd³⁺- and Tb³⁺- doped particles were synthesized following the same procedure and using neodymium nitrate hydrate (Nd(NO₃)₃·xH₂O, Sigma Aldrich, 99.9%) and terbium nitrate hydrate (Tb(NO₃)₃·5H₂O, Sigma Aldrich, 99.9%). Doping levels used varied from 0.25 to 2.5 mol% Nd³⁺ and from 5 to 30 mol% Tb³⁺.

2.2. Characterization techniques

The shape and size of the particles was examined by *transmission electron microscopy* (TEM, Philips 200CM working at 200 kV). A droplet of an aqueous suspension of the samples was deposited on a copper grid coated with a transparent polymer and dried. Particle size distributions were obtained from the micrographs by counting several hundreds of particles, using the free software *ImageJ*. Mean values were then calculated and given followed by the standard deviation between parenthesis. Additional

information on the size and colloidal stability of the particles in aqueous suspension (0.5 mg·mL⁻¹ of solid) was obtained from *Dynamic Light Scattering (DLS)* measurements. The experiments were carried out using a Malvern Zetasizer Nano-ZS90 equipment, which was used as well to measure the Zeta potential of the suspensions.

The crystalline structure of the prepared particles was assessed by *X-ray diffraction (XRD)* using a Panalytical, X'Pert Pro diffractometer (CuK α) with an X-Celerator detector over an angular range of $10^\circ < 2\theta < 120^\circ$, 2θ step width of 0.02° , and 10 s counting time. Silicon was used as internal standard. The TOPAS software (TOPAS version 4.2, Bruker AXS, 2009) was used to calculate the unit cell volume of the cerium fluoride structure using the Rietveld method.^[25] Refined parameters were background coefficients, scale factor, zero, unit cell parameters, displacement parameters of Ce³⁺ and profile parameters. The isomorphic substitution of Nd³⁺ or Tb³⁺ by Ce³⁺ in the cerium fluoride crystal structure was proved as well by determination and comparison of unit cell parameters of the undoped samples with both the Nd³⁺- and the Ce³⁺-doped nanoparticles.

To gain additional information on the morphological and structural features of the synthesized nanoparticles, they were also characterized by *High Angle Annular Dark Field Scanning TEM* (HAADF-STEM) and *High Resolution TEM*. The samples were deposited in a copper grid as in the case of the Philips 200CM described above. A FEI Tecnai field emission gun STEM microscope (G2F30) working at 300 kV (0.2 nm point resolution) and equipped with a HAADF detector from Fischione (0.16 nm point resolution in STEM-HAADF mode) was used. A Fischione ultra-narrow gap tomography holder was used to acquire HAADF-STEM images from 0° to 70° . The *Digital Diffraction Patterns* (DDP) were obtained from the HRTEM images using the *Tecnai Imaging and Analysis* (TIA) software. No sample damage was appreciated during the measurements.

The *excitation and emission spectra* of the Tb³⁺-doped CeF₃ nanoparticles dispersed in water (0.5 mg·mL⁻¹) were measured in a Horiba Jobin Yvon spectrofluorimeter (Fluorolog3). The excitation/emission slits used to record the excitation and emission spectra were 1 nm/5 nm and 5 nm/1 nm, respectively. All the spectra were recorded using 1 nm steps. Tb³⁺ decay curves were recorded on powder samples in the same fluorimeter, using a pulsed lamp with a $\lambda_{\text{exc}} = 257$ nm and recording the luminescence decay at $\lambda_{\text{em}} = 540$ nm, associated to the $^5\text{D}_4 \rightarrow ^7\text{F}_5$ transition. The emission spectra were transformed to the CIE color coordinates system using a 2° observer.

The *emission spectra* of the Nd³⁺-doped CeF₃ nanoparticles were recorded under continuous wave (CW) excitation using a CW diode laser @ 810 nm as excitation source. For that purpose, the powder samples were placed filling a tiny hole (3 mm diameter) practiced in an aluminum foil and sandwiched between two microscope slides. This arrangement allows not only keeping an approximately constant amount of sample, but also preserving the geometry for reproducible luminescence measurements. Fluorescence was analyzed through an ARC monochromator model SpectraPro 500-i and then detected using an AsGaIn photodiode. Nd³⁺ lifetime measurements were obtained using the pulsed excitation provided by the second harmonics of a Nd:YAG laser ($\lambda_{\text{ex}} = 532$ nm) and recording the luminescence decay at $\lambda_{\text{em}} = 1056$ nm, associated to the $^4F_{3/2} \rightarrow ^4I_{11/2}$ transition. The signal was recorded and averaged using a Tektronix DPO4104B-L digital oscilloscope.

For the evaluation of the CT contrast efficiency, aqueous dispersions containing different concentrations of the CeF₃ nanoparticles and Iohexol (Sigma Aldrich, analytical standard, $\geq 95\%$) in 1.5 mL Eppendorf tubes were prepared. These dispersions were placed in a vortex device for 2 min prior to analyses. Each sample (200 μ L aliquot) was placed in a multiwell microplate, along with a MilliQ water sample for calibration. CT images were acquired with a NanoSPECT/CT® (Bioscan), located at the Centro Nacional de Aceleradores (CNA, Sevilla, Spain). Acquisition parameters included a 106 mA current for a voltage of 75 kV, exposure time per projection of 1500 ms and 360 projections per rotation. The image length was 6 cm, with a pitch of 1. The total acquisition time required was 18 min. The image was reconstructed with Vivoquant image processing software (Invicro), with the exact cone beam filtered back projection algorithm and the Shepp Logan 98 % filter. The resulting image pixelsize was uniform in three dimensions at 0.2mm. Images were analyzed with PMOD 3.8 software (PMOD Technologies LLC). Spherical volumes of interest (VOIs) of 2 mm radius were made within each sample to calculate the X-ray attenuation (in Hounsfield Units, HU) for each concentration. Average values of Milli-Q water and dispersions were used to calculate HU values in the images, with attenuation being 0 HU for water and -1000 HU for air.

3. Results and Discussion

3.1. Synthesis and morphology of undoped CeF₃ nanoparticles

To synthesize uniform and water-dispersible CeF₃ based NPs, the homogeneous precipitation method was selected here using polyols as solvent due to the known ability of these alcohols to act not only as solvents but also as capping agents, thus limiting particle growth.²⁶ Homogeneous precipitation can be achieved by a controlled release of anions, cations or both to get similar kinetics of precipitation throughout the solution.²⁷ For the synthesis of lanthanide fluoride materials, fluoride anions can be released in a controlled manner by using certain precursors containing the [BF₄]⁻ anion, which slowly hydrolyzes liberating free fluoride anions into the solution.²⁸ Therefore, the presence of a certain amount of water is required in this case. On the other hand, the controlled release of lanthanide cations can be achieved by decomposition on heating of lanthanide complexes such as those obtained from acetate anions.^[29] It has also been demonstrated that the synthesis of uniform particles through homogeneous precipitation requires a precise reaction kinetics, which is governed by the synthesis parameters such as solvent nature, reagent nature, reagent concentration, temperature, etc. Finding the precise set of experimental parameters that allow obtaining uniform particles demands a trial and error methodology by systematically varying just one synthesis parameters and keeping the rest constant.

For simplicity, we first addressed the synthesis of undoped CeF₃ using the controlled release of fluoride anions approach from a solution of cerium nitrate and sodium tetrafluoroborate in polyol/water mixtures. Following such methodology, we found that aging at room temperature, for 20 hours, a solution containing Ce(NO₃)₃ (0.05 M) and NaBF₄ (0.18 M) in a mixture of EG/H₂O (90/10 V/V) gave rise to uniform, well dispersed round particles as those shown in the TEM micrograph of **Figure 1a**. The darker elongated particles in the micrograph could likely correspond to particles standing with their rounded face perpendicular to the grid plane, from where particles with a lenticular shape and an estimated thickness of ~20 nm could be inferred, as it will be later substantiated. **Figure 1b** shows the histogram obtained by measuring the diameter of a hundred particles in TEM micrographs, which indicated an average value of 55(10) nm. Based on the lenticular shape of the NPs and on their diameter value, they will be called LNP-55 from now on. The hydrodynamic diameter obtained from the DLS plot recorded on an aqueous suspension of the NPs (**Figure 1c**) was 60(20) nm. This value is very close to the diameter obtained from TEM measurements and shows the absence of particle aggregation. The Zeta potential value obtained in the same aqueous suspension (pH =5.3)

was 43.1(0.9) mV, which indicates that the particles dispersion is caused by electrostatic repulsion forces. This is a clear advantage, in terms of green chemistry, of the synthesis method reported in this paper compared to those using surfactants,^[30] complexing agents^[31] or polymers^[21] to inhibit particle aggregation

Several experimental parameters were found to be critical to produce uniform particles. For example, changing the EG/H₂O ratio to any value below 9/1, while keeping all the other parameters fixed, led to either heterogeneous or aggregated particles (**Figure S1**). This result can be assigned to the different viscosity and dielectric constant of the resulting solvent mixture that affects the reaction kinetics. Other parameters resulted to be less crucial to obtain uniform NPs. For example, they could be obtained from [BMIM]BF₄ instead of NaBF₄ (**Figure S2a**) which is reasonable given that, in both cases, the reaction kinetics is controlled by the release of fluoride ions from the same species ([BF₄]⁻). However, the use of NH₄F or HF as the fluorine source led to different heterogeneous precipitates (**Figure S2b and S2c**, respectively) as expected from the lack of controlled release of fluoride ions in both cases. On the other hand, the concentration of Ce(NO₃)₃ and NaBF₄ did not result to be a critical factor to obtain uniform NPs, as long as an excess fluoride concentration in relation to CeF₃ stoichiometry was maintained. **Figure S3a** shows the NPs obtained after doubling the Ce(NO₃)₃ and NaBF₄ concentrations with respect to those used in Figure 1a, while **Figure S3b** shows the result of halving both concentrations. In both cases, the morphology of the resulting particles was the same as in Figure 1a. The use of stoichiometric amounts of Ce and F, that is Ce/F = 1/3, led however to the formation of rather homogeneous but almost double sized particles (100 nm diameter), as shown in the TEM micrograph and histogram of **Figure S3c**. Finally, the change of the Ce³⁺ precursor to CeCl₃ (which is completely dissociated in the solvent, as was the case of Ce(NO₃)₃) resulted in very similar particles to those obtained from the nitrate salt (**Figure S4a**), while an amorphous precipitate was observed when cerium acetate was used as the Ce precursor (**Figure S4b**). This result suggests that the reaction kinetics associated to the simultaneous controlled release of both, cations (from acetate salt) and anions (from NaBF₄) is not adequate to form uniform particles. All the above mentioned effects must be assigned to variations in the kinetics of precipitation induced when altering the experimental conditions, which affect the nucleation and growth processes.^[32]

Interestingly, when all experimental parameters used to synthesize the NPs shown in Figure 1a were kept constant and the ethylene glycol was replaced by diethylene glycol, smaller lenticular NPs were obtained, as shown in **Figure 1d**. Also in this case the elongated darker particles could correspond to particles standing with their round face perpendicular to the grid, from where a particle thickness of ~30 nm could be estimated. The histogram of **Figure 1e** shows an average particle diameter of 40(10) nm, while the hydrodynamic diameter obtained from the DLS curve recorded on an aqueous suspension of the NPs (**Figure 1f**) was 60(20) nm, which indicates a very subtle aggregation of the NPs in the suspension. The Zeta potential measured in an aqueous suspension (pH = 5.3) of the as-synthesized NPs was in this case 49.6(2.1) mV, which also indicates the dispersion of the NPs in water was due to electrostatic repulsive forces. These particles will be called LNP-40 from now on.

Finally, when 1,3-butanediol was used in the polyol/H₂O mixture, keeping constant all the other experimental parameters used to synthesize the NPs of Figure 1a, bigger (80 nm diameter) and transparent rounded particles were obtained (**Figure 1g**). A discoidal shape can be inferred from their transparency as well as from the width (~10 nm) of the elongated dark particles observed in the same micrograph, which might correspond to particles standing with their flat face perpendicular to the grid. The DLS curve shows in this case, an average hydrodynamic diameter of 82(20) nm, in very good agreement with the values obtained from TEM micrographs, which indicates the absence of particles aggregation. The Zeta potential value measured in an aqueous suspension of these NPs was 40.9(1.1) mV, which also points out to the presence of positive charges on the NPs surface which inhibit their aggregation by repulsive forces. These NPs will be called DNP from now on.

The colloidal stability of the NPs in physiological media was analysed through DLS measurements conducted in MES buffer (50 mM, pH = 6). The value of the hydrodynamic diameters measured on MES suspensions of LNP40, LNP55 and DNP samples were close to 100 nm in all three cases, which indicates a certain aggregation of the NPs in this medium.

To confirm that the elongated particles observed in all three micrographs of Figure 1a, 1d and 1g are lateral views of the particles, we have taken HAADF-STEM images of the three types of NPs at two different orientations of the TEM sample holder (0° and 70°) (**Figure 2**). With the holder at 0°, specific regions of the grid were selected that contained

exclusively round particles, as can be observed in the top images of Figure 2a (LNP-55), Figure 2b (LNP-40) and Figure 2c (DNP). The round LNP-55 and DNP clearly transformed into elongated ones when the holder was tilted at 70°. This effect was not observed in the LNP-40, which indicates that these NPs are more isometric, as already inferred from the TEM micrograph of Figure 1d. In addition, it is to be noticed that the widths of all three NPs observed at 70° are slightly larger than those observed in Figure 1 as the holder could only be tilted up to 90°.

Table 1 contains a summary of the three types of uniform nanoparticles synthesized with their morphology and dimensions.

3.2. Crystal structure and microstructure of lentil-like and discoidal CeF₃ nanoparticles

The crystal structure as well as the microstructure of LNP-55, LNP-40, and DNP samples was analyzed using X-ray diffraction and high-resolution transmission electron microscopy. **Figure 3** shows the XRD patterns of the three types of NPs synthesized. All of them show the same set of reflections, which match well with PDF 00-008-045 (ICDD, 2016) corresponding to hexagonal CeF₃. A detailed observation of the pattern of DNP shows a clear anisotropic peak broadening with reflections 110 and 300 (corresponding to the planes parallel to the *c* axis) showing narrower peak width than the rest of reflections in the pattern. This effect is less pronounced on the LNP-55 pattern and it is absent on the LNP-40 pattern, the latter exactly matching the intensity ratios observed on the PDF. This observation indicates that the crystallites forming the DNP and, to a lower extent, the LNP-55, possess a high aspect ratio, with bigger crystallite dimensions in the direction perpendicular to the 110 and 300 planes. Crystallite sizes were calculated for the three types of NPs using the Scherrer formula from the peak width of the 300 and 113 reflections. **Figure S5** shows the experimental and fitted patterns used to obtain the full width at half maximum of the reflections and **Table 2** shows the obtained crystallite sizes and their aspect ratio for each sample as well as the aspect ratio obtained from the particles dimensions. All crystallite size values calculated resulted to be smaller than the particles size themselves, which is an indication of the polycrystalline character of the particles. Secondly, the crystallite size obtained from the 300 reflection was 3 times higher than that from 113 in DNP, while it was only double in LNP-55 and the same value from 300 and 113 was observed for the LNP-40 case. The aspect ratio obtained from both crystallite size values were similar to the aspect ratio obtained from the particle dimensions in all three cases, which suggests

that the particles growth is driven by an orientated attachment of their constituting crystallites.^[33]

To shed more light on the NPs microstructure, they were analyzed using HRTEM images, which clearly show lattice fringes for all three NPs types, thus revealing their high crystallinity (**Figure 4a, 4b and 4c**). The individual crystallites showed a DDP compatible with the hexagonal CeF_3 structure in all three cases (**Figure 4d, 4f and 4h**). The DDP calculated from the whole NP in LNP-55 and DNP samples (**Figure 4e and 4i**) exhibit relatively well defined spots that confirm the oriented attachment of the constituent crystallites commented above. The DDP of a whole LNP-40 (**Figure 4g**) showed, however, more elongated spots, indicating a lower degree of crystallites orientation. The zone axis of the DDPs is, in all three cases, $[001]$ indicating that the c crystallographic axis of the hexagonal CeF_3 unit cell is perpendicular to the flat face of the NPs. This orientation is in good agreement with the XRD data, which indicated that the crystallites forming DNP and LNP-55 showed the biggest dimension in the direction perpendicular to the c axis.

3.3. Synthesis and structure of $\text{Tb}:\text{CeF}_3$ and $\text{Nd}:\text{CeF}_3$ nanoparticles

Among the three morphologies of CeF_3 nanoparticles synthesized in this work, the LNP-40 were selected for doping as a proof of concept due to their smaller dimensions, which are more adequate for biotechnology applications, as described in the introduction of this work. The synthesis method used to obtain LNP-40 at room temperature was also successful to obtain CeF_3 NPs doped with different concentrations of Tb^{3+} (5, 10, 20 and 30 mol%) and Nd^{3+} (0.5, 1.0, 1.5, and 2.0 mol%). The morphology and size of the doped NPs did not changed respect to the undoped ones except for the case of the 30% Tb doped NPs which showed a slightly higher diameter, as shown in **Table S1**. To check the effective substitution of Nd^{3+} and Tb^{3+} for Ce^{3+} on the CeF_3 crystal structure, XRD patterns were recorded on the doped samples and compared with the undoped sample. The XRD patterns of the different Tb^{3+} - and Nd^{3+} -doped NPs were very similar to each other and to those of the undoped material and no extra reflections could be observed at any doping level for any dopant ion (**Figure S6**). The hexagonal CeF_3 crystal structure was therefore preserved during the doping processes. Slight shifts of the reflections were observed on the patterns because of the different ionic radii of Ce^{3+} , Tb^{3+} and Nd^{3+} . The unit cell parameters of Tb- and Nd-doped samples were calculated using the Rietveld method. The obtained unit cell volume values (**Table S1**) were plotted in **Figure 5**. In

both cases, shrinkage of the unit cell volume is observed with increasing doping concentration, as expected from the lower ionic radii of Tb^{3+} (1.040 Å in VIII coordination) and Nd^{3+} (1.109 Å in VIII coordination) in comparison to Ce^{3+} (1.143 Å in VIII coordination). The volume decrease is linear with Tb and Nd concentration, which indicates the formation of ideal solid solutions. Finally, the slope of the line that defines the volume decrease in the Tb case is more pronounced than in the Nd case as expected from the bigger difference in ionic radii between Ce^{3+} and Tb^{3+} than between Ce^{3+} and Nd^{3+} .

3.4. Luminescence properties of the Tb:CeF₃ nanoparticles

The excitation spectrum of 5% Tb:CeF₃ LNP-40 monitored at the 540 nm emission ($^5\text{D}_4 \rightarrow ^7\text{F}_5$) of Tb^{3+} (**Figure 6a**) shows an intense excitation band centered at 257 nm, which corresponds to the transitions from the ground state $^2\text{F}_{5/2}$ of Ce^{3+} to the different components of the excited Ce^{3+} 5d states.^[34] The observation of this band, while monitoring the Tb^{3+} emission, is a clear indication of the energy transfer process from Ce^{3+} to Tb^{3+} ions. Several excitation bands showing much lower intensity can also be observed between 310 nm and 400 nm (magnified red curve in Figure 6a), which correspond to the direct 4f-4f transitions of Tb^{3+} , the most intense appearing at 351 nm. The much lower intensity of the Tb^{3+} excitation bands is due to the fact that the transitions from Tb^{3+} $^7\text{F}_6$ ground state into the higher excited states are parity-forbidden, in contrast to the optically allowed 5d-4f transition of Ce^{3+} ions. The emission spectrum obtained while exciting the 5% Tb:CeF₃ LNP-40 sample at 351 nm (red curve in **Figure 6b**) shows characteristic emissions at 487 nm, 540 nm, 582 nm and 619 nm arising from electron transitions from the $^5\text{D}_4$ excited state of Tb^{3+} to the lower lying levels $^7\text{F}_J$ ($J = 6, 5, 4, 3$). The emission bands exhibit a very poor signal to noise ratio which is increased by a factor of 2500 when the excitation is carried out at 257 nm (blue curve in Figure 8b), thus confirming the $\text{Ce}^{3+} \rightarrow \text{Tb}^{3+}$ energy transfer. **Figure S7** shows the energy level diagrams of Ce^{3+} and Tb^{3+} , showing the energy transfer process. The intense band at 540 nm is responsible for the green color of the sample, as observed in the CIE triangle shown as an inset of Figure 8b, where the CIE coordinates (0.27, 0.59) obtained from the emission spectrum of the sample have been plotted.

In order to study the effect of Tb concentration on the luminescence of the CeF₃ NPs and determine the optimum concentration of Tb ions, we have first recorded emission spectra (using an excitation wavelength of 257 nm) on four colloidal suspensions containing the

same weight amount of LNP-40 nanoparticles doped with 5%, 10%, 20% and 30% Tb (**Figure 6c**). It can be observed that increasing Tb content from 5% to 20% gave rise to an increase of the emission intensity, which can be assigned to an increase in the number of emitting centers. Further increasing the Tb content to 30 %, however, did not result in a further increase of the emissions, likely as a consequence of the well-known concentration quenching effect.^[12] This effect is more clearly shown in **Figure 6d** where the integrated area between 450 nm and 650 nm of the emission spectra of Figure 8c has been plotted versus Tb content. The optimum value for Tb doping is therefore 20 mol%, which is very close to those reported in the literature for CeF₃:Tb NPs with other morphologies and sizes.^[12,14,21]

Luminescence decay curves corresponding to the $^5D_4 \rightarrow ^7F_5$ transition of Tb³⁺ ions in CeF₃ LNP-40 doped with different amounts of Tb³⁺ ions are presented in **Figure 6e**. All curves could be successfully fitted to a bi-exponential decay function according to Equation (1):

$$I(t) = I_1 \exp(-t/\tau_1) + I_2 \exp(-t/\tau_2) \quad (1)$$

where $I(t)$ is the luminescence intensity, t is the time after excitation, and τ_i ($i = 1, 2$) is the decay time of the i component, with intensity I_i . The corresponding fitting parameters are summarized in **Table 3** along with the average decay times, $\langle \tau \rangle$, defined as:

$$\langle \tau \rangle = \frac{\int_{t_0}^{t_f} t I(t) dt}{\int_{t_0}^{t_f} I(t) dt} = (\tau_1^2 I_1 + \tau_2^2 I_2) / (\tau_1 I_1 + \tau_2 I_2) \quad (2)$$

The long lifetime has classically been assigned to the luminescent centers located in the interior of the nanoparticle while the short lifetime values correspond to the surface ions, where the presence of impurities such as hydroxyl species, act as luminescence quenchers, thus increasing the decay rate.^[35] The average lifetime values (**Figure 6f**) remain approximately constant for [Tb] $\leq$ 20% while a significant decrease is observed when [Tb] = 30%, thus confirming the concentration quenching effect that takes place at [Tb] > 20 %, as inferred from the emission spectra described above. The lifetime values reported in the literature for CeF₃:Tb NPs are either similar to those found in this work (up to 6.36 ms)^[20] or smaller (down to 3.48ms),^[30] which suggest a high luminescence efficiency of the synthesized Tb-CeF₃ NPs.

Their luminescence, together with their uniform nanosize, water-disperse character and colloidal stability make the synthesized Tb:CeF₃ NPs especially interesting for *in-vitro* bio-applications that demand an intense fluorescence bioprobe emitting in the visible range of the spectrum, where most of the imaging equipment used in bio-medicine have their spectral response optimized. However, as commented in the introduction of this paper, the UV wavelength needed to excite the emission of the Tb³⁺ ions make these NPs less useful for *in vivo* applications. For this reason, we have proceeded to dope the same NPs with Nd³⁺ ions, which allow excitation and emission in the biological windows and are therefore, appropriate for *in vivo* imaging.

3.5. Luminescence properties of the Nd:CeF₃ nanoparticles

The emission spectra of Nd:CeF₃ LNP-40 containing different amounts of Nd³⁺ (0.25, 0.50, 1.0 and 2.0%) were recorded using a continuous wave diode at $\lambda_{\text{exc}} = 810$ nm (**Figure 7a**). As observed in **Figure S8** excitation at 810 nm populates the ⁴F_{5/2}:²H_{9/2} multiplet of Nd³⁺, which then populates the ⁴F_{3/2} state via non-radiative relaxation, from where the different near infrared (NIR) emissions originate. The emission spectra of the samples showed, consequently, emissions at ~875 nm, ~1056 nm and ~1325 nm, corresponding, respectively, to the transitions from the excited ⁴F_{3/2} level of Nd³⁺ ions to the ⁴I_{9/2}, ⁴I_{11/2} and ⁴I_{13/2} lower lying levels. The emission intensity increased with increasing Nd content, the most intense emission being observed for the highest doping level of this study (2%). The integrated area of the spectra has been plotted in **Figure 7b**, where an almost linear increase can be observed at low Nd contents and a slight depart from linearity becomes evident at [Nd] = 2 %, which suggests a concentration quenching effect at this composition.

The dynamics of the Nd³⁺ luminescence was analyzed from the decay curves corresponding to the ⁴F_{3/2} → ⁴I_{11/2} electronic transition, which gave quantitative information about the [Nd³⁺] at which the maximum emission intensity is expected for each NP type. The curves were recorded for all the Nd-doped samples using the pulsed excitation provided by the second harmonics of a Nd:YAG laser ($\lambda_{\text{ex}} = 532$ nm). Excitation at 532 nm populates the ²G_{7/2} level of Nd³⁺, which then populates the ⁴F_{3/2} state via non-radiative relaxation, from where the different near infrared (NIR) emissions originate (see energy levels diagram in Figure S8). Consequently, the decay curves of the different Nd-doped CeF₃ samples (**Figure 7c**) show a rise at the very beginning of the detection period,

which corresponds to the filling of the emitting $^4F_{3/2}$ level from the upper $^2G_{7/2}$ level, convoluted with the temporal response of the detection system. The decay curves showed, after the initial rise, an exponential decay that could be fitted using a bi-exponential temporal dependence (Equation 1) for all the samples. The corresponding fitting parameters are summarized in **Table 3**. The average lifetime (calculated following Equation 2 and plotted in **Figure 7d**) shows a slight decrease at low Nd contents and a more pronounced drop at $[\text{Nd}^{3+}] = 2\%$, which indicates the presence of concentration quenching at this doping level, in agreement with the behavior of the integrated area of the emission spectra *vs.* Nd content analyzed above.

3.6. X-ray attenuation properties of the CeF_3 nanoparticles

The high atomic number of lanthanides make the Nd-doped CeF_3 NPs potentially useful as contrast agents in X-ray Computed Tomography (CT) as it is well known that materials possessing high Z tend to better absorb X-rays.⁴ To proof this hypothesis, we selected the 2% Nd-doped CeF_3 LNP-40 sample that was the most appropriate for *in vivo* purposes, as described above. The X-ray absorption values of aqueous suspensions containing different concentrations of the 2% Nd: CeF_3 nanoparticles were measured and compared with aqueous suspensions containing the same concentrations of Iohexol, a clinically approved CT contrast agent. The corresponding CT phantom images are shown in **Figure 8a**, where a higher contrast can be observed for the nanoparticles suspensions than for Iohexol at any concentration. The X-ray absorption values obtained, in Hounsfield units (HU), are shown in **Figure 8b**. Good linear correlations between the HU values and the concentration of the suspensions are observed for both Nd: CeF_3 NPs and Iohexol. The slope of the curve was significantly higher for the CeF_3 NPs than for Iohexol. To obtain enough contrast in the CT image, the local X-ray attenuation change with the contrast should be about 100 HU. We can see from the Figure 12b that to achieve this we need about 10 mg/mL of iodine local concentration and only 5 mg/mL of NPs. As quantities used in CT imaging to inject in bolus of Iohexol are high, the lowering of the concentration by half is an important factor and reveals the superior CT imaging performance of the NPs as promising CT contrast agents.

4. Conclusions

We successfully synthesized uniform, water-dispersible CeF₃ nanoparticles with three different shapes and tunable size via a facile precipitation method at room temperature. The synthesis method consisted of the aging, at room temperature for 20 hours, a solution containing cerium nitrate and sodium tetrafluoroborate in a mixture of a certain polyol and water (90/10 V/V). Lentil-like NPs were obtained when the polyol used was either ethylene glycol or diethylene glycol, the particles dimensions being smaller in the latter case. When 1,3-butanediol/H₂O was used as the solvent, keeping all other experimental parameters fixed, discoidal NPs were obtained. As demonstrated for the smaller NPs, synthesized in the presence of diethylene glycol, CeF₃ NPs could be doped with different concentrations of both Tb³⁺ and Nd³⁺ ions to make them useful as luminescent bioprobes with different purposes. The Tb³⁺-doped CeF₃ NPs demonstrated to be excellent green phosphors thanks to the excitation through the Ce-Tb energy transfer band, with potential use for *in-vitro* biolabelling applications. The Nd:CeF₃ NPs, on the other hand, showed emission in the near infrared after excitation at 810 nm, which is interesting for deep tissue fluorescence bioimaging. Finally, the doped CeF₃ NPs showed a higher X-ray absorption coefficient than Iohexol, as shown for the Nd system, which proved their capability to be used as promising contrast agents in X-ray computed tomography. In summary, we have developed a commercially attractive procedure to prepare dual luminescent and CT bioprobes consisting of uniform, water dispersible Tb:CeF₃ and Nd:CeF₃ nanoparticles at room temperature, which considerably facilitates their large scale production versus other synthesis methods reported in the literature that require the use of mid or even high temperatures or surfactants.^{20,21} Extension of this synthesis procedure to other lanthanide fluoride-based NPs is the subject of future work.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at

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Table 1: Shape and dimensions of the three types of CeF₃ NPs obtained after aging at room temperature for 20 hours a solution containing Ce(NO₃)₃ (0.05 M) and NaBF₄ (0.18M) in different polyol/H₂O (90/10 V/V) mixtures. DEG = Dyethylene glycol, EG= ethylene glycol, BG= 1,3-butanediol.

Polyol	Sample name	Morphology		Dimensions (Diameter/thickness)
		Front view	Lateral view	
DEG	LNP-40			40 nm/30 nm
EG	LNP-55			55 nm/20 nm
BG	DNP			80 nm/10 nm

Table 2: Crystallite size (nm) calculated using Scherrer Equation on the 300 and 113 reflections of the XRD patterns corresponding to LNP-55, LNP-40 and DNP samples.

Sample	300	113	300/133 ratio	Aspect ratio of the NP (from TEM)
LNP-55	13	6	2.2	2.7
LNP-40	9	9	1	1.3
DNP	20	4	5	8

Table 3: Fitting parameters of the bi-exponential temporal dependence for the luminescence decay curves of the Tb³⁺:CeF₃ and Nd³⁺:CeF₃ nanophosphors recorded at the dominant emission of the Tb³⁺ ion with an excitation wavelength of 257 nm and of the Nd³⁺ ion with an excitation wavelength of 532 nm. Mind the different units for Tb and Nd lifetimes. (Estimated error 5%)

% Tb ³⁺	τ_1 (ms)	I_1 (%)	τ_2 (ms)	I_2 (%)	$\langle\tau\rangle$ (ms)
5	1.7	35	6.4	65	5.8
10	1.7	32	6.3	68	5.8
20	1.9	31	5.7	71	5.2
30	0.68	43	3.2	57	2.8
% Nd ³⁺	τ_1 (μ s)	I_1 (%)	τ_2 (μ s)	I_2 (%)	$\langle\tau\rangle$ (μ s)
0.25	38	79	130	21	82
0.5	41	78	128	22	81
1	46	82	130	18	78
2	46	88	130	12	70

Figure 1: TEM micrographs, histograms showing NPs diameter obtained from TEM micrographs and DLS plots corresponding to CeF₃ LNP-55 (*left*), LNP-40 (*middle*) and DNP (*right*) (See Table 1 for samples identification).

Figure 2: HAADF-STEM images of CeF₃ LNP-55 (*a*), LNP-40 (*b*) and DNP (*c*), recorded at 0° and 70° tilt angles.

Figure 3: XRD pattern corresponding to CeF₃ LNP-55 (*a*), LNP-40 (*b*) and DNP (*c*). PDF 00-008-045, corresponding to hexagonal CeF₃ is shown at the bottom.

Figure 4: HREM images of CeF_3 LNP-55 (*a*), LNP-40 (*b*), and DNP (*c*). *d*, *f*, and *h*) DDPs calculated from the red square on each top image. *e*, *g* and *i*) DDPs calculated using the image of the whole NP.

Figure 5: Unit cell volume versus Tb³⁺ and Nd³⁺ content in CeF₃ LNP-40. Error bars are equivalent to symbols size.

Figure 6: *a)* Excitation spectrum corresponding to 5% Tb:CeF₃ LNP-40, recorded at an emission wavelength of 540 nm. *b)* Emission spectra of 5% Tb:CeF₃ LNP-40 recorded with two different excitation wavelengths 257 nm (blue curve) and 351 nm (red curve). *c)* Emission spectra corresponding to LNP-40 samples doped with different Tb concentrations, recorded with an excitation wavelength of 257 nm. *d)* Integrated area of the emission spectra of Tb:CeF₃ LNP-40 samples *versus* Tb content. *e)* Temporal evolution of the ⁵D₄ → ⁷F₅ (540 nm) luminescence for the CeF₃ LNP-40 nanophosphors doped with different amounts of Tb³⁺ (excitation at 257 nm). *f)* Average lifetime $\langle\tau\rangle$ calculated from the right hand-side term of Equation (2), using the corresponding fitting parameters given in Table 3, vs. Tb content for the CeF₃ NPs.

Figure 7: *a)* Emission spectra of Nd-doped CeF₃ LNP-40. *b)* Integrated area between 825 nm and 1450 nm, of the spectra shown in *a*. *c)* Temporal evolution of the ⁴F_{3/2}–⁴I_{11/2} luminescence for the CeF₃ LNP-40 nanophosphors doped with 0.25, 0.5, 1.0, and 2.0 mol% Nd³⁺. *d)* Average lifetime (τ) calculated from the right hand-side term of Eqn (2), using the corresponding fitting parameters given in Table 3, vs. Nd content.

Figure 8: a) CT phantom images of Nd:CeF₃ LNP-40 and Iohexol at different concentrations in water. b) HU values against the concentration of Nd:CeF₃ NPs and Iohexol.

Supplementary material

Room Temperature Synthesis of Water-dispersible $\text{Ln}^{3+}:\text{CeF}_3$ (Ln= Nd, Tb) Nanoparticles with Tunable Morphology as Bimodal Probes for Fluorescence and CT Imaging.

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Figure S1: Top: TEM micrographs of the particles obtained after aging, at room temperature for 20 hours, a solution containing $\text{Ce}(\text{NO}_3)_3$ (0.05 M) and NaBF_4 (0.18M) in different mixtures of ethylene glycol/ H_2O : a) 0% H_2O ; b) 10% H_2O ; c) 20% H_2O ; c) 30% H_2O ; d) 100% H_2O . Bottom: DLS plots of the particles shown above.

Figure S2: TEM micrographs of the samples synthesized in the same experimental conditions as those of LNP-55 simple, changing exclusively the fluoride precursor nature: *a)* [BMIM]BF₄; *b)* NH₄F; *c)* HF.

Figure S3: TEM micrographs and histograms, showing particles diameter, of the samples synthesised in the same experimental conditions as those of LNP-55, changing exclusively the precursors concentrations:

- a) $[Ce(NO_3)_3] = 0.025\text{ M}$ and $[NaBF_4] = 0.09\text{ M}$
- b) $[Ce(NO_3)_3] = 0.1\text{ M}$ and $[NaBF_4] = 0.36\text{ M}$
- c) $[Ce(NO_3)_3] = 0.05\text{ M}$ and $[NaBF_4] = 0.0375\text{ M}$

Figure S4: TEM micrographs of the samples synthesized in the same experimental conditions as those of LNP-55 sample, changing exclusively the cerium precursor nature: *a)* CeCl_3 ; *b)* $\text{Ce}(\text{OOCCH}_3)_3$

Figure S5: Selected region of the experimental (black curves) and fitted (red curve) XRD patterns of DNP (top) LNP-55 (middle), LNP-40 (bottom) samples showing the two individual contributions (Green curves) to each profile, corresponding to the 300 (left) and 113 (right) reflections.

Figure S6: XRD patterns of CeF₃ LNP-40 doped with different Tb contents (top) and Nd contents (bottom). Asterisks indicate reflections from Silicon standard used to calibrate the patterns.

Figure S7: Electron energy levels of Ce^{3+} and Tb^{3+} ions showing the Ce-Tb energy transfer.

Figure S8: Energy level diagram of 4f electrons in Nd³⁺ showing the transitions expected after excitation at 532 nm and 808 nm and the emissions from the $^4F_{3/2}$ level. The zig-zag curve represents non-radiative emissions from the upper levels to the emitting $^4F_{3/2}$ level.

Table S1: NP diameter and unit cell parameters of CeF₃ LNP-40 samples doped with different Tb and Nd concentrations. Standard deviations are given in parenthesis.

Doping Ln ³⁺	Molar % Ln ³⁺	NP diameter (nm)	a (Å)	c (Å)	Volume (Å ³)
none	0	40(10)	7.1270(4)	7.2790(8)	320.20(5)
Tb ³⁺	5	42(10)	7.1106(5)	7.2613(9)	318.80(6)
	10	41(10)	7.1016(5)	7.2545(9)	316.85(6)
	20	44(10)	7.0839(5)	7.2272(9)	314.10(6)
	30	52(10)	7.0653(5)	7.2099(9)	311.69(6)
Nd ³⁺	1	39(10)	7.1255(5)	7.2789 (8)	320.02(6)
	2	41(10)	7.1243(5)	7.2788(8)	319.99(6)