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Facile fabrication of biodegradable lanthanide ions containing fluorescent polymeric nanoparticles: Characterization, optical properties and biological imaging

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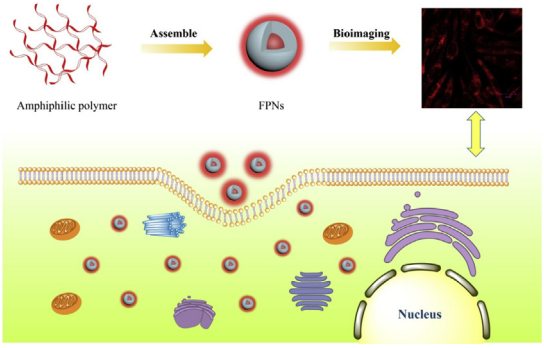
HIGHLIGHTS

- Lanthanide ions containing fluorescent polymeric nanoparticles.
- These FPNs are water soluble and biodegradable.
- These FPNs are fabricated through a two-step conjugation reaction.
- These FPNs are promising for biological applications.

GRAPHICAL ABSTRACT



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ABSTRACT

The fluorescent polymeric nanoparticles (FPNs) with encapsulated europium complexes have recently emerged as one of the most promising luminescent probes for biomedical applications owing to their unique optical properties, biocompatibility and structure designability. Significant progresses have been made for the preparation of biocompatible trivalent lanthanide ions (Ln^{3+}) fluorescent nanoparticles, whereas, only limited attention was focused on the fabrication of europium ion containing FPNs with biodegradability, high sensitivity and deep penetration. In this work, a facile and simple method was developed to construct biodegradable and biocompatible luminescent polyurethanes (PUs) through a two-step polymerization. In this construction system, diisocyanate-terminating polyethylene glycol (NCO-PEG-NCO) was first synthesized and subsequently conjugated with dihydroxyl modified europium (III) chelates ($Eu(TTA)_3Phen$-OH) to obtain these luminescent PUs. These PUs show amphipathic property and can assemble into core-shell FPNs in aqueous solution and exhibit high water dispersibility. Biological evaluation results suggest that $Eu(TTA)_3Phen$-PEG_{2000} FPNs possess desirable biocompatibility and great potential for biological imaging applications. Therefore, we expect that the fabrication approach will inspire much research enthusiasm and effort for the preparation of biodegradable luminescent probes.

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1. Introduction

Fluorescent labeling has been deemed as a powerful tool in many fields of cell biology studies and biomedicine [1–4]. In the past decades, numerous fluorophores, such as organic dyes, fluorescent proteins, quantum dots (QDs), and fluorescent polymeric nanoparticles (FPNs) have received significant attentions for use in biological sensing and imaging applications [5–11]. These applications are however often restricted by the inherent chemical, photophysical and biological drawbacks of fluorescent labels. Furthermore, the rational design of luminescent probes with improved properties is a pursuit of great interest. Trivalent lanthanide ion (Ln^{3+}) complexes have aroused tremendous interest in bioanalysis and bioimaging because of their unique luminescence features, such as long lifetimes, large Stokes shift, sharp emission lines and superior photostability [12–16]. Especially probes contain europium (III) ion are considered to be captivating candidates combine the advantages of high sensitivity and deep penetration. In particular, europium chelates with suitable light-harvesting ligands have characteristic of high luminescence quantum yields [17,18]. However, unmodified europium chelates show poor dispersibility in water. For the biomedical applications, the purpose is first to ensure good water dispersion of europium complex, therefore, functional modification of europium complex is an essential step. Especially, cellular membrane permeability is regarded as one of the most desired prerequisites for study of europium composites in biomedical applications. In order to address these problems, the development of biocompatible and biodegradable luminescent polymeric probes by incorporating europium complexes into hydrophilic polymer matrices has attracted increasing research interest.

The rational design of biocompatible and biodegradable polymers for development of novel biomedical applications has become one of the hot research topics [19–21]. As a versatile type of polymers, polyurethanes (PUs) have been widely used in various fields due to their low toxicity, biocompatibility and tunable structures [22–24]. The physicochemical and mechanical properties of PUs can be easily tailored by adjusting relative compositions of hard and soft segments, which can further extend their applicable scopes and fit diversity applications. PUs with tailored biocompatibility and mechanical performance are considered as suitable candidates for applications such as soft tissue engineering and drug delivery carriers [25–27]. Over the past years, studies focused on amphiphilic assemblies have evolved from adjusting molecule structures to obtain well-defined morphologies and incorporation with functional components to prepare smart nanomaterials [28–30]. Among them, polymeric amphiphiles have attracted great attention for their enhanced kinetic and thermodynamic stability [31]. Therefore, self-assembly micelles based on biocompatible and biodegradable amphiphilic PUs have been developed for nanoprobes or anticancer drug delivery vehicles in recent years. Polyethylene glycol (PEG) is one of the most popular hydrophilic polymers, and has been extensively utilized for construction of PUs by incorporating as soft segments or end capping agents. The water solubility of hydrophobic europium chelates can be improved by physical encapsulation while the biocompatible PEG coating can stabilize the bioprobes in an aqueous medium as well as prolong blood circulation time by rendering the particles high resistance to protein adsorption [32–34]. Although considerable efforts have been devoted to developing novel PEG functionalized biocompatible nanomaterials, only limited research has focused on the fabrication of biodegradable lanthanide ions containing FPNs.

In this report, we prepared the polymeric probes based on europium (III) chelates with excellent biocompatible and biodegradable properties. The amphipathic luminescent PUs were synthesized via a two-step polymerization. The detailed procedures were displayed in Scheme 1, the diisocyanates terminating PEG pre-polymer was first prepared. In the next step, dihydroxyl modified europium (III) chelates were added to pre-polymer as chain extender. The obtained amphiphiles were self-assembled into luminescent micelles in aqueous solution. Due to the unique luminescence features of europium (III) ion complexes, such lanthanide ion (III) complexes containing FPNs show great potential for cell imaging applications.

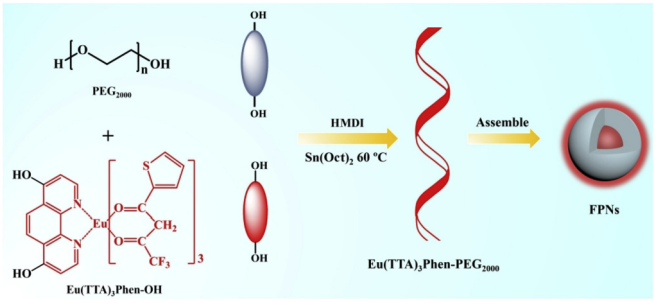
2. Experimental procedures

2.1. Materials and characterization

All of the chemical agents and solvents were obtained from commercial sources and used as received. Europium (III) chloride hexahydrate ($EuCl_3 \cdot 6H_2O$), 2-Thenoyltrifluoroacetone (TTA), 4,7-dihydroxy-1,10-phenanthroline (Phen-OH), hexamethylene diisocyanate (HMDI), PEG_{2000} and stannous octoate were purchased from Aladdin Chemistry Co. Ltd. (Shanghai, China). ^1H nuclear magnetic resonance (NMR) spectra were recorded on Bruker Avance-400 spectrometer with $CDCl_3$ as the solvent. The synthetic europium (III) chelates and FPNs were characterized by Fourier transform infrared spectroscopy (FT-IR) using KBr pellets. FT-IR spectra were supplied from Nicolet 5700 (Thermo Nicolet corporation). Transmission electron microscopy (TEM) images were recorded on a Hitachi 7650B microscope operated at 80 kV, the TEM specimens were got by putting a drop of $Eu(TTA)_3Phen\text{-}PEG_{2000}$ FPNs on a carbon coated copper grid. F-4500 FL spectrophotometer with a slit width of 5 nm was used to test fluorescence spectra of FPNs in water. The X-ray photoelectron spectra (XPS) were collected on a VGESCALAB 220-IXL spectrometer using an Al Kα X-ray source (1486.6 eV). All binding energy (BE) values were calibrated using the containment carbon (C1s = 284.6 eV).

2.2. Preparation of $Eu(TTA)_3Phen$-OH complexes

The $Eu(TTA)_3Phen$-OH complexes were prepared according to previous works [35]. A solution of $EuCl_3$ (366.4 mg $EuCl_3 \cdot 6H_2O$) and TTA (666 mg) which both dissolved in ethanol were stirred at room temperature for 10 min. Subsequently, Phen-OH (212 mg) dissolved in ethanol was added. After 30 min, the solution pH value was adjusted to 7 by adding sodium hydroxide solution. And then, the mixture was heated to 55 °C and stirred for 5 h. After the reaction completed, pouring the solution into deionized water and a large amount of the yellow crude product occurred. The desired product was collected by filtration and washed with deionized water for 3 times and dried in vacuum drying oven 40 °C to yield $Eu(TTA)_3Phen$-OH. Yield: 72%.



Scheme 1. Schematic showing the fabrication of biocompatible and biodegradable $Eu(TTA)_3Phen\text{-}PEG_{2000}$ FPNs.