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Reverse microemulsion synthesis of layered gadolinium hydroxide nanoparticles

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ABSTRACT

A reverse microemulsion approach has been explored for the synthesis of layered gadolinium hydroxide (LGdH) nanoparticles in this work. This method uses oleylamine as a multifunctional agent, acting as surfactant, oil phase and base. 1-butanol is additionally used as a co-surfactant. A systematic study of the key reaction parameters was undertaken, including the volume ratio of surfactant (oleylamine) to water, the reaction time, synthesis temperature, and the amount of co-surfactant (1-butanol) added. It proved possible to obtain pristine LGdH materials at temperatures of 120 °C or below with an oleylamine: water ratio of 1:4. Using larger amounts of surfactant or higher temperatures caused the formation of $Gd(OH)_3$, either as the sole product or as a major impurity phase. The LGdH particles produced have sizes of ca. 200 nm, with this size being largely independent of temperature or reaction time. Adjusting the amount of 1-butanol co-surfactant added permits the size to be varied between 200 and 300 nm.

1. Introduction

Ion-exchangeable layered materials have attracted widespread attention for a broad range of applications. Materials able to exchange both cations and anions are known [1], with the latter having been more widely studied [2,3]. In both cases, the incorporation of guest ions into the interlayer space of the host materials can have a number of benefits: for instance, the stability of guest species can be improved by intercalation [4,5].

One family of materials which has been particularly extensively studied is the layered double hydroxides (LDHs) [2]. LDHs comprise positively-charged mixed-metal hydroxide layers, with charge-balancing anions in the interlayer region [2]. A large variety of inorganic and organic anions can be incorporated into their interlayer space by ion-exchange reactions [6–8]. This rich intercalation chemistry has been extensively exploited: LDHs have been investigated for applications such as flame retardants [9,10], catalysts and catalyst precursors [11], CO_2 adsorbents [12–16], cement additives [17] and drug delivery systems [7,18–20]. Bioactive molecules have been intercalated into the interlayer space of LDHs on a number of occasions. Examples include non-steroidal anti-inflammatory drugs such as naproxen, diclofenac, gemfibrozil, ibuprofen and 2-propylpenpenoic acid [7,19]. There are also reports of the encapsulation of anticancer drugs (e.g. 5-fluorouracil and methotrexate) [21,22]. LDH-drug intercalates have been found to lead to sustained drug release profiles and reduced side effects compared to the free drug [7,19].

Beyond LDHs, there exists a range of alternative layered materials capable of anion exchange. These include the recently reported layered rare-earth hydroxides (LRHs). There are a range of LRHs possible, but those capable of anion exchange have the general formula $[R_2(OH)_5]^+(A^{n-})_{1/n}{\cdot}yH_2O$ (where R = Ln^{3+}, A^{n-} = an anion, and $1 \leq y \leq 2$). Such LRHs contain lanthanide cations and hydroxide ions in their positively charged layers, and charge-balancing anions in the interlayer region [23–25]. Typical examples include $[Gd_2(OH)_5]Cl{\cdot}1.5H_2O$ and $[Yb_2(OH)_5]Cl{\cdot}1.5H_2O$ [3]. The inorganic anions typically present in the gallery of LRHs immediately after synthesis can be readily replaced by other inorganic or organic species such as azamacrocyclic crown ether [26], or amino acids [27].

LRHs could thus be potent alternatives to LDHs for use as, for instance, drug delivery systems. Moreover, LRHs possess the magnetic and fluorescent properties of the rare-earth metals they contain, which could give additional benefits. The combination of ion exchange intercalation chemistry and rare earth elements in the layers can lead to integrated materials with many applications in medical science [28,29], catalysis [30], separation science [26], sensor technologies [31], and luminescence devices [5,27,32–40]. Some studies have

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focused on incorporating sensitizers or quenchers to tune the colour emission of LRH hybrids, for instance [3,5,27].

Magnetic resonance imaging (MRI) is a technique widely used in biomedical imaging. It is popular in part because it does not use radioactive agents or high-energy electromagnetic waves, and has high spatial and temporal resolution [41]. To obtain good quality images, however, the patient must be administered what is termed a "contrast agent", a chemical entity used to enhance the quality of the images obtained and permit accurate diagnoses. Commercial contrast agents are commonly based on Gd^{3+}. This is because the electronic relaxation time of Gd^{3+} is very long and it has a high number of unpaired electrons, which means that it can enhance both the longitudinal (r_1) and transverse (r_2) relaxation times of water protons [42]. Free Gd^{3+} is extremely toxic, and thus the agents used in the clinic are based on chelation complexes designed to ensure that the Gd present remains complexed at all times. An alternative route to preclude free Gd^{3+} getting into solution is to incorporate it into an inorganic matrix, and hence layered gadolinium hydroxides (LGdHs) might be viable contrast agents [43]. The potential of LGdHs in this regard has been explored in several reports [28,29,43,44], and the results obtained are promising. The LGdH matrix has also attracted a little attention for use as a drug delivery system, with the intercalation of several pharmaceutically active molecules including antibiotics, amino acids, and microRNA [43,45].

Control of particle size can be extremely important to achieve the desired results in vivo, and for this reason much attention has been paid in particular to the production of nanoscale materials, which have been explored in many fields [46]. The size of LDH particles has been shown to play an important role in their interactions with cells, for instance [47]. Therefore, controlling the particle size of LGdH will be important to ensure uptake by cells, and thus to improve its performance in MRI or drug delivery applications. However, little effort has been applied to the synthesis of LRH nanoparticles to date.

One route to control particle size is the use of reverse microemulsion systems. These comprise water droplets dispersed in an oil continuous phase; when materials are grown from an aqueous solution, performing the reaction in such systems means that the particle size is controlled by the size of the droplets, so long as the emulsion is stable and there is no coalescence. This approach has been found to lead to high degrees of control over particle size, morphology, geometry, and surface area [46], and microemulsion systems have emerged as an effective method to synthesize nanomaterials such as metallic catalysts [48], semiconductors [49], ceramics [50], and silica [51]. Here, we apply this approach for the first time to the synthesis of nanosized LGdH materials, aiming to produce particles with sizes suitable for cellular uptake. We report the synthesis of LGdH nanoparticles using a method in which oleylamine acts as oil phase, base and surfactant, permitting an extremely simple microemulsion formulation to be employed.

2. Experimental

2.1. Materials

Oleylamine and 1-butanol were purchased from Sigma-Aldrich (Gillingham, UK), while gadolinium chloride hexahydrate was supplied by Alfa Aesar (Heysham, UK). All water used was deionized, and all other chemicals were of analytical grade and used without further purification.

2.2. Methods

2.2.1. General protocol

A novel reverse microemulsion method which employs oleylamine as oil phase, base and surfactant was developed in 2012 to synthesize LDHs [47]. Experiments were carried out following this method with minor modifications. A 0.5 M solution of $GdCl_3{\cdot}6H_2O$ in deionized water was first prepared, and to this a mixture of oleylamine and 1-butanol was added dropwise with vigorous stirring. After 10 min of constant stirring, the resultant mixture was transferred to a Telfon-lined stainless steel autoclave (23 mL) and treated hydrothermally. The resulting precipitates were collected by centrifugation, washed with a mixture of water and ethanol (1:1, v/v), and dried at 40 °C for one day.

2.2.2. Optimization

A detailed optimization process was undertaken in this work. First, since the volume ratio of surfactant to water is known to be a determining factor for particle size [47,52], a range of oleylamine: water ratios were explored (4:1, 3:2, 1:3 and 1:4). Specifically, 8, 6, 2.5 or 2 mL of oleylamine was first combined with 5 mL of 1-butanol. The resultant mixtures were added to 2, 4, 7.5 or 8 mL of a 0.5 M Gd chloride solution. The total volume of oleylamine and water was kept at 10 mL, and the total solution volume in the autoclave was 15 mL. Hydrothermal treatment was undertaken at 120 °C for 18 h. The resulting samples are denoted as LGdH-O*m*-W*n* (*m* = volume of oleylamine, *n*= volume of water).

Second, the temperature was optimized. With an increase in temperature in a hydrothermal process, the particle size of the product tends to be larger [51]; however, high temperatures could also lead to potential degradation or phase transformation. The surfactant to water volume ratio was set to 1:4, and each reaction mixture comprised 2 mL oleylamine, 5 mL 1-butanol, and 8 mL Gd chloride solution. Hydrothermal treatments were carried out at temperatures ranging from 90 °C to 150 °C for 18 h. The products are denoted LGdH-90 °C, LGdH-120 °C, and LGdH-150 °C.

Third, the aging duration is another factor which could determine the particle size: the longer the crystals grow, the larger they will be. A volume ratio of surfactant to water of 1:4 was used, and again each reaction mixture comprised 2 mL oleylamine, 5 mL 1-butanol, and 8 mL Gd chloride solution. LGdH nanoparticles were prepared with hydrothermal treatment at 12 h, 18 h or 24 h at 120 °C. The products were named LGdH-12 h, LGdH-18 h, and LGdH-24 h.

Finally, the co-surfactant amount in water-in-oil microemulsion systems has been reported to have an important effect on particle growth, with nanoparticle size rising with an increasing amount of co-surfactant [51]. Hence, the volume of 1-butanol was varied from 3 to 9 mL. The ratio of surfactant to water was fixed at 1:4, so each reaction mixture comprised 2 mL of oleylamine, 8 mL of Gd chloride solution, and between 3 and 9 mL of 1-butanol. Experiments were carried out at 120 °C for 12 h. The materials obtained were designated LGdH-3 mL, LGdH-5 mL, LGdH-7 mL and LGdH-9 mL.

2.3. Characterization

2.3.1. X-ray diffraction (XRD)

Power XRD patterns were recorded over the 2θ range from 3 to 45° on a Rigaku MiniFlex 600 diffractometer (Tokyo, Japan), using Cu Kα radiation (λ = 1.5418 Å) at 40 kV and 15 mA.

2.3.2. Fourier transform infrared (FTIR) spectroscopy

Infrared spectra were obtained using a Spectrum 100 FTIR spectrometer (Perkin Elmer, Waltham, MA, USA) over the range 650–4000 cm^{-1} with a resolution of 2 cm^{-1}.

2.3.3. Dynamic light scattering (DLS)

Dynamic light scattering measurements were performed on a Zetasizer Nano ZS instrument (Malvern Instruments, Malvern, UK). 1–2 mg of LGdH nanoparticles was suspended in ethanol and sonicated for ca. 15 min prior to measurements.

2.3.4. Transmission electron microscopy (TEM)

LGdH nanoparticles (5 mg) were dispersed in ethanol (1 mL), followed by 20 min of sonication. A few drops of each suspension were