Liquid Marbles Based on Magnetic Upconversion Nanoparticles as Magnetically and Optically Responsive Miniature Reactors for Photocatalysis and Photodynamic Therapy

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Abstract: Magnetic liquid marbles have recently attracted extensive attention for various potential applications. However, conventional liquid marbles based on iron oxide nanoparticles are opaque and inadequate for photo-related applications. Herein, we report the first development of liquid marbles coated with magnetic lanthanide-doped upconversion nanoparticles (UCNPs) that can convert near-infrared light into visible light. Apart from their excellent magnetic and mechanical properties, which are attractive for repeatable tip opening and magnetically directed movements, the resultant UCNP-based liquid marbles can act as ideal miniature reactors for photodynamic therapy of cancer cells. This work opens new ways for the development of liquid marbles, and shows great promise for liquid marbles based on UCNPs to be used in a large variety of potential applications, such as photodynamic therapy for accelerated drug screening, magnetically guided controlled drug delivery and release, and multifunctional actuation.

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Lanthanide-doped upconversion nanoparticles (UCNPs), a class of new luminescent nanomaterials that convert two or more low-energy near-infrared (NIR) photons into high-energy photons for UV/Vis emissions, normally consist of transition-metal, lanthanide, or actinide dopant ions embedded in the lattice of an inorganic crystalline host. Among them, hexagonal-phase sodium yttrium fluoride (NaYF₄) is the most efficient host material for producing green (Yb³⁺/Er³⁺ co-doped) and blue (Yb³⁺/Tm³⁺ co-doped) upconversion phosphors. Magnetic UCNPs can also be prepared by doping with Gd³⁺ to obtain optically and magnetically active bifunctional materials for advanced multifunctional devices.

Herein, we describe the preparation of optically and magnetically active bifunctional UCNP-based liquid marbles by doping NaYF₄ nanocrystals with Yb³⁺/Er³⁺/Gd³⁺ in a facile hydrothermal process. The constituent UCNPs were functionalized with polyhedral oligomeric silsesquioxane (POSS) to make the particles highly hydrophobic, which is required for the formation of liquid marbles. The resultant UCNP-based liquid marbles were exposed to NIR illumination to generate visible emission (i.e., green luminescence) for initiating photoinduced reactions inside the liquid marbles.
to produce reactive oxygen species (ROS) from protoporphyrin IX (PpIX), followed by photodynamic therapy of cancer cells in situ. Thus this work describes a novel application for liquid marbles and a new approach for photodynamic therapy.

The Yb\(^{3+}/\)Er\(^{3+}/\)Gd\(^{3+}\)-doped NaYF\(_4\) upconversion nanoparticles were synthesized by well-developed hydrothermal synthetic methods using oleic acid as the surfactant. According to a previously reported procedure, the Yb\(^{3+}\), Er\(^{3+}\), and Gd\(^{3+}\) dopant concentrations in the UCNPs were adjusted to 18, 2, 50 mol\%, respectively, to obtain nanoparticles with a highly crystalline hexagonal phase for efficient upconversion luminescence. Figure 1b shows a typical transmission electron microscopy (TEM) image of the resultant UCNPs, which reveals the average size of the UCNPs to be 100–200 nm in length and 20–50 nm in width. The presence of surface carboxyl groups on the UCNPs nanoparticles allowed for further surface modification with amino-functionalized POSS molecules by amide formation to form hydrophobic UCNP-POSS nanoparticles (Figure 1a). The UCNP/POSS weight ratio in the UCNP-POSS nanoparticles was determined by thermogravimetric analysis (TGA) to be about 3:1 (Figure 1c). As can be seen in the Supporting Information, Figure S6, a UCNP-POSS film containing red-colored water (containing cell-culture medium, see below) was used in Figure 2e for the demonstration of the magnetic-field-induced tip opening. The ability to undergo magnetic-field-induced opening could enable the opened liquid surface to wet a contacting glass capillary, and it could thus be used for transferring liquid into or out of the liquid marble (Figure S9). For ease of visualization, a liquid marble containing red-colored water (containing cell-culture medium, see below) was used in Figure 2e for the demonstration of the magnetic-field-induced tip opening. The ability to undergo magnetic-field-induced opening could enable the opened liquid surface to wet a contacting glass capillary, and it could thus be used for transferring liquid into or out of the liquid marble (Figure S9). For ease of visualization, a liquid marble containing red-colored water (containing cell-culture medium, see below) was used in Figure 2e for the demonstration of the magnetic-field-induced tip opening. The ability to undergo magnetic-field-induced opening could enable the opened liquid surface to wet a contacting glass capillary, and it could thus be used for transferring liquid into or out of the liquid marble (Figure S9). For ease of visualization, a liquid marble containing red-colored water (containing cell-culture medium, see below) was used in Figure 2e for the demonstration of the magnetic-field-induced tip opening. The ability to undergo magnetic-field-induced opening could enable the opened liquid surface to wet a contacting glass capillary, and it could thus be used for transferring liquid into or out of the liquid marble (Figure S9). For ease of visualization, a liquid marble containing red-colored water (containing cell-culture medium, see below) was used in Figure 2e for the demonstration of the magnetic-field-induced tip opening. The ability to undergo magnetic-field-induced opening could enable the opened liquid surface to wet a contacting glass capillary, and it could thus be used for transferring liquid into or out of the liquid marble (Figure S9).
Liquid marbles have recently been used for the formation of cancer cell spheroids as the three-dimensional cell cultures in liquid marbles more closely resemble the in vivo physiology of tumors than two-dimensional cell cultures. For the first time, we performed a study on the photodynamic therapy of cancer cells by incubating cells inside the UCNP liquid marbles, along with PpIX as a ROS generator, and using the upconversion nanoparticle coating to provide the required irradiation (Figure 4a). Figures 4b shows a digital photograph of a liquid marble formed from an aqeous suspension of MAD-MD-231 cells (200 µL) and UCNP-POSS.
powder, and Figure 4c shows an optical microscopy image of MAD-MD-231 cells. Apart from the photodynamic therapy of cells inside the liquid marbles, control experiments were also carried out, in which cells were cultured in normal culture dishes with and without PpIX and/or UCNP-POSS nanoparticles (Figure 4d). MTT studies were then performed to determine the cell viabilities (Figure S16). To investigate the distribution of cells within the liquid marble, the UCNP-POSS powder from a deliberately broken cell-encapsulating liquid marble was imaged with an optical microscope. No cells were observed in the UCNP-POSS powder from the broken liquid marble (Figure S17), suggesting that the cells were well-dispersed inside the liquid marble rather than sedimented on or stuck to the inner surface of the UCNP-POSS shell. Figure S18 gives the results from the MTT test for the MAD-MD-231 cells inside the liquid marbles with and without PpIX, which showed decreased cell viability with increasing exposure time to a 980 nm laser in the presence of PpIX, indicating NIR-induced photodynamic therapy of the cancer cells. For the cells inside the liquid marbles without PpIX, however, NIR light irradiation had no significant effect on cell viability. In control experiments, NIR exposure under the same conditions caused a decrease in cell viability for the MAD-MD-231 cells in the culture dish with both PpIX and UCNP-POSS powder (IV in Figures 4d,e), but not for the same cells inside culture dishes that do not contain both PpIX and UCNP-POSS powder (I–III in Figures 4d,e). Owing to the large contact area between the UCNP-POSS powder coating and the cell culture media as well as the spherical geometry to enable 360° irradiation, the PpIX-encapsulating UCNP-based liquid marbles exhibited a much more efficient photodynamic therapy compared to the same treatment performed with the two-dimensional culture dishes (sample VI vs. IV in Figures 4d,e). Both cells incubated with UCNP-POSS powder in a culture dish (III) and cells incubated in a liquid marble without PpIX (V) exhibited high viability, demonstrating that the marble shell material had low toxicity. Therefore, the observed reduced cell viability in sample VI could be confidently attributed to the photodynamic therapy. Although these preliminary results on photodynamic therapy of cancer cells inside the UCNP liquid marbles could be further improved by optimizing the experimental conditions (e.g., the liquid marble size/shell thickness, the cell and/or drug concentrations, and the irradiation intensity), these results clearly indicate that liquid marbles based on upconversion nanoparticles provide important advantages for biomedical studies, particularly for accelerating drug screening for the photodynamic therapy of cancer cells.

In summary, we have described the advantages of using lanthanide-doped upconversion nanoparticles as encapsulating powders to prepare optically and magnetically active bifunctional liquid marbles. By chemical bonding of POSS to the surface of Yb3+/Er3+/Gd3+ doped NaYF4 UCNPs, we prepared superhydrophobic UCNP-POSS composite nanoparticles as coatings for the formation of liquid marbles from water droplets. The resultant liquid marbles based on UCNP-POSS and water exhibited excellent mechanical stability, magnetic properties, and were able to convert low-energy near-infrared photons into high-energy UV/Vis photons. These unique properties, in combination with the associated three-dimensional cell cultures and three-dimensional optical emission (irradiation), render these UCNP-based liquid marbles ideal miniature reactors for studying the photodynamic therapy of cancer cells inside the liquid marbles with NIR irradiation. We believe that liquid marbles based on UCNPs show great promise for a large variety of applications, including, but not limited to, photodynamic therapy for accelerated drug screening, magnetically controlled drug delivery and release, and multifunctional actuation.

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All rolled into one: Liquid marbles based on magnetic upconversion nanoparticles (UCNPs) exhibit excellent magnetic and mechanical properties and were used for the conversion of low-energy near-infra-red photons into high-energy UV/Vis photons. They might find application in photodynamic therapy as well as for magnetically controlled drug delivery and release and multifunctional actuation.