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Magnetic field activated lipid–polymer hybrid nanoparticles for stimuli-responsive drug release

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ABSTRACT

Stimuli-responsive nanoparticles (SRNPs) offer the potential of enhancing the therapeutic efficacy and minimizing the side-effects of chemotherapeutics by controllably releasing the encapsulated drug at the target site. Currently controlled drug release through external activation remains a major challenge during the delivery of therapeutic agents. Here we report a lipid–polymer hybrid nanoparticle system containing magnetic beads for stimuli-responsive drug release using a remote radio frequency (RF) magnetic field. These hybrid nanoparticles show long-term stability in terms of particle size and polydispersity index in phosphate-buffered saline (PBS). Controllable loading of camptothecin (CPT) and Fe_3O_4 in the hybrid nanoparticles was demonstrated. RF-controlled drug release from these nanoparticles was observed. In addition, cellular uptake of the SRNPs into MT2 mouse breast cancer cells was examined. Using CPT as a model anticancer drug the nanoparticles showed a significant reduction in MT2 mouse breast cancer cell growth *in vitro* in the presence of a remote RF field. The ease of preparation, stability, and controllable drug release are the strengths of the platform and provide the opportunity to improve cancer chemotherapy.

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1. Introduction

Nanotechnology for medical applications is an exciting and rapidly advancing field with a significant impact on diagnosis and therapeutics for the treatment of human diseases [1–7]. Nanoparticle-based drug delivery is of particular interest for cancer treatment, owing to such features as a prolonged circulation half-life, reduced non-specific uptake, and increased tumor accumulation through enhanced permeation and retention (EPR) or active targeting [8–10]. Currently over 20 nanoparticle-based therapeutics have been approved for clinical use and numerous products are under clinical testing [11–13]. Among these clinical or pre-clinical products liposomes and biodegradable polymeric nanoparticles are the most widely adopted carriers for drug delivery [14,15]. More recently lipid–polymer hybrid nanoparticles [16–20] have been developed by combining both liposomes and polymeric nanoparticles into a single delivery system. The resulting lipid–polymer hybrid nanostructure gives rise to unique advantages, such as ease of particle preparation, improved functionalizability, and more sustained drug release kinetics. These lipid–polymer hybrid nanoparticles have proven to be a robust platform in which different modalities can be incorporated for precision drug delivery [18].

The allure of on demand drug release, which promises enhanced therapeutic efficacy through targeted delivery, has motivated the development of stimuli-responsive delivery systems triggered by acidity, temperature, magnetic fields, and light irradiation [21–27]. Previously we presented a hollow silica nanocapsule capable of on–off switchable drug release via application of a remote radio frequency (RF) magnetic field [23]. Herein a one step nanoprecipitation process was used to prepare 80 nm lipid–polymer hybrid nanoparticles co-encapsulating 10 nm magnetic beads and a model anticancer drug, camptothecin (CPT). The nanocarrier platform possesses numerous advantages, including ease of preparation, sustained drug release, and excellent stability under physiological conditions [28,29]. The hydrophobic polymeric core of the platform readily encapsulated the water-insoluble drug for systemic delivery. The lipid coating provided a diffusional barrier that retards drug release in the absence of an external stimulus [28]. Upon RF magnetic field actuation localized heating by Fe_3O_4 inside the polymeric cores loosened the polymer matrices and accelerated drug release, resulting in increased cytotoxicity *in vitro* against a

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mouse breast cancer cell line. Taking advantage of the robust lipid–polymer hybrid carrier platform we demonstrate the preparation of lipid–polymer hybrid nanoparticles for controlled drug release through a single step nanoprecipitation procedure, and also demonstrate stimuli-responsive drug release from such nanoparticles as well as their – cytotoxicity to cancer cells.

2. Materials and methods

2.1. General comments

All reagents were purchased from Sigma–Aldrich Inc. and Alfa Aesar, and used without further purification. The microscopic characterization of synthesized nanoparticles was carried out using a transmission electron microscope (FEI Tecnai G2 Sphera at 200 keV acceleration voltage). Various chemical and optical measurements were performed using a UV/vis spectrophotometer (Thermo BioMate3). To generate the RF magnetic field a Lepel LSS-2.5 RF power supply equipped with a water-cooled solenoid was used.

2.2. Synthesis of ~10 nm iron oxide nanoparticles

Monodisperse Fe_3O_4 nanoparticles were prepared according to a previous report [22]. Briefly, a mixture of 24 g $FeCl_3{\cdot}6H_2O$ and 9.82 g $FeCl_2{\cdot}4H_2O$ was reacted with 50 ml of ammonium hydroxide under nitrogen gas at 80 °C, and then the solution was allowed to react for 1.5 h after the addition of 3.76 g oleic acid. The prepared magnetite nanoparticles were washed with deionized water until the pH was neutral and subsequently transferred in situ into tetrahydrofuran (THF).

2.3. Synthesis of iron oxide-loaded lipid–polymer hybrid nanoparticles

Iron oxide-loaded lipid–polymer hybrid nanoparticles, herein designated stimuli-responsive nanoparticles (SRNPs), were prepared via self-assembly of poly(lactic-co-glycolic acid) (PLGA) having a glass transition temperature T_g of ~45 °C (Lactel, Pelham, AL) [30], refined soybean lecithin (molecular weight ~330 Da, Alfa Aesar, Ward Hill, MA), carboxyl-terminated 1,2-distearoyl-sn-glycero-3 phosphoethanolamine-N-carboxy(polyethylene glycol) (DSPE-PEG), and iron oxide nanoparticles through a single step nanoprecipitation method. Briefly, 0.12 mg lecithin and 0.26 mg DSPE-PEG were dissolved in 2 ml of 4 wt.% aqueous ethanol solution. The solution was heated to 68 °C to better disperse the lipid components. In parallel, 1 mg PLGA polymer and 400 μg iron oxide nanoparticles were dissolved in 1 ml of THF. The resulting PLGA solution was then dropwise added to the lipid solution under gentle stirring. The mixed solution was vortexed vigorously for 3 min, followed by gentle stirring for 3 h at room temperature. Following solvent evaporation the remaining organic solvent, free molecules, and unencapsulated iron oxide nanoparticles were removed by washing the SRNP solution three times using an Amicon Ultra-4 centrifugal filter (Millipore, Billerica, MA) with a molecular weight cut-off (MWCO) of 100 kDa. Removal of unencapsulated iron oxide nanoparticles (typically ~10 nm diameter) was verified through dynamic light scattering (DLS) measurements, which revealed a unimodal particle population 80 nm in diameter.

2.4. Characterization of stimuli-responsive nanoparticles

The SRNP size (diameter in nm) and polydispersity index (PDI) were measured by DLS using a Nano-ZS model ZEN3600 (Malvern, UK). The SRNPs (~500 μg) were dispersed in water (~1 ml) and the measurements were performed in triplicate at room temperature. The size and PDI of the SRNPs in water at room temperature were monitored for 30 days.

2.5. Measurement of CPT loading in stimuli-responsive nanoparticles

The SRNPs were prepared with different initial concentrations of CPT or iron oxide nanoparticles. To quantify the drug loading the SRNPs were dried and 1 ml of THF was added. The resulting solution was stirred for 3 h and subsequently filtered twice in 2 K MWCO Slide-A-Lyzer Cassettes (Millipore, Bellerica, MA) placed in an Eppendorf tube at 1500 r.p.m. for 5 min. Using non-CPT-loaded nanoparticles as the baseline control, the drug loading yield in the lipid–PLGA hybrid nanoparticles was quantified based on the absorbance at 362 nm as measured with a UV/vis spectrophotometer (Thermo BioMate3) following a previously published protocol [31].

2.6. Drug release characterization

For the drug release study 5 wt.% CPT-loaded SRNPs were prepared and then remote RF activated drug release was measured by UV/vis spectrophotometry. First, a 100 μl solution containing 5% CPT-loaded SRNPs was loaded on a 2K MWCO Slide-A-Lyzer filter. The filter was then inserted into a tube containing 1 ml deionized water. The resulting solution was exposed to RF (at 100 kHz) for 8 min twice, with a 4 min interval in between. A multiple RF exposure schedule was chosen so as to release a sufficient amount of drug with minimal risk of overheating and possible changes in the particle characteristics. The resulting drug concentration in the 1 ml solution was measured using UV/vis spectrophotometry and calibrated using a standard with predefined CPT concentrations. Following data collection the SRNP solution was placed in another tube containing 1 ml of fresh water. Cumulative CPT release was monitored at 37 °C for ~50 h. The study was performed in triplicate.

While our drug delivery experiments with tumor cells were performed in serum, our long-term storage stability studies were performed in PBS. A similar trend in stability is anticipated in serum-based solutions. In fact, we have already demonstrated that similar lipid–polymer hybrid nanoparticles (similar lipid and PLGA formulations, but without the magnetic nanoparticles embedded within the PLGA in the present work) remain stable in a serum environment over a relevant blood circulation period of 24 h [29].

2.7. Cellular internalization study

For the cellular internalization study 0.5 μg of a hydrophobic DiD dye was added to the solvent mixture containing 400 μg iron oxide nanoparticles prior to SRNP preparation following a previously published protocol [32]. The solvent mixture was added dropwise to an aqueous mixture of lecithin and DSPE-PEG. Following 3 h solvent evaporation the particles were washed in Amicon filters prior to use. The murine breast cancer cell line MT2 was maintained in Dulbecco's modified Eagle's medium (Gibco-BRL, Grand Island, NY) supplemented with 10% fetal calf serum (FCS) (Hyclone, Logan, UT), penicillin/streptomycin (Gibco-BRL), L-glutamine (Gibco-BRL), MEM non-essential amino acids (GibcoBRL), sodium bicarbonate (Cellgro, Herndon, VA), and sodium pyruvate (Gibco-BRL). The cells were cultured at 37 °C with 5% CO_2 and plated in chamber slides (Cab-Tek II, eight wells, Nunc, Rochester, NY) with the aforementioned medium. On the day of the experiment MT2 cells were washed with prewarmed PBS and incubated with prewarmed medium for 30 min before adding 100 μg Fe_3O_4-loaded nanoparticles stained with DiD dyes. The nanoparticles were incubated with the cells for 40 min at 37 °C, washed three times with PBS, fixed with tissue fixative (Millipore, Bellerica, MA) for 15 min at room temperature and stained with 4′,6-diamidino-2-phenylindole (DAPI) (nuclear staining). The cells were then

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