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ORIGINAL PAPER

A thermo/pH/magnetic-responsive nanogel based on sodium alginate by modifying magnetic graphene oxide: Preparation, characterization, and drug delivery

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Abstract
A novel thermo/pH/magnetic-triple-responsive nanogel was synthesized by grafting *N*-isopropylacrylamide and acrylic acid onto sodium alginate to modify magnetic graphene oxide as a drug delivery system. The synthesized nanogel was characterized by scanning electron microscopy (SEM), dynamic light scattering (DLS), vibrating sample magnetometer (VSM), atomic force micrographs (AFM), Fourier transform infrared spectroscopy (FTIR), and thermogravimetric analysis (TGA). The obtained nanogel displayed excellent reversible transmittance changes in response to pH, temperature, and magnetic field. The performance of the nanogels to load doxorubicin (DOX) drug and to sustain doxorubicin release was tested upon exposure to pH, temperature, and magnetic field variations. The mechanism of drug release was proposed in this paper by different kinetic models. In addition, the effects of nanogels and DOX-loaded nanogels on MCF-7 cells were examined and results were compared with free DOX drug. The in vitro results demonstrated that this triple-responsive nanogel can be an appropriate candidate for applications in cancer therapy.

Keywords Triple-responsive nanogel · Magnetic graphene oxide · Sodium alginate · Drug release · Cytotoxicity

Introduction

Within the last decade, nanogels received tremendous attention for targeted biomedical applications and controllable release [1–3]. Nanogels are soft nanoscopic particles with three-dimensional networks of cross-linked flexible hydrophilic polymers [2]. Nanogels have high porous structure and swell in aqueous solution as hydrogel [3]. They can also encapsulate drug, oligonucleotides, and imaging agents inside their cross-linked network and protect them against possible environmental degradation [4, 5]. The cross-linked structure of nanogels is usually responsive to environmental changes such as pH, redox conditions, temperature, enzyme activity, competitive binding, magnetic actuation, and photo-irradiation [6–8]. The stimuli such as: pH, temperature, and magnetic responsiveness are the most frequently used for on-demand drug release and reduce premature drug release at non-desirable sites [7–9]. In addition, response of nanogels to more than one stimulus can even further improve drug delivery [10]. This can be achieved by incorporating materials into the nanogels that make them responsive to stimuli relevant [11]. The temperature-responsive nanogels were usually obtained by poly(*N*-isopropylacrylamide) (PNIPAM). Nanogel-based PNIPAM displays lower critical solutions temperatures (LCST) at near physiological temperature [6]. Below this temperature, the PNIPAM nanogels are swollen through hydrophobic forces present along the isopropyl side chains and hydrocarbon backbone [8]. However, the PNIPAM nanogel collapses at high LCST owing to the loss in hydrogen bonding and weakness of the hydrophobic forces. This unique behavior makes PNIPAM nanogels as a best carrier to retain drug at body temperature (~ 37 °C), and rapidly deliver the drug within a locally heated tumor (~ 40–42 °C) [9, 10]. Moreover, the presence of pH-sensitive bonds in the nanogel can lead to control drug delivery in specific organs (such as the gastrointestinal tract or the vagina), intracellular compartments (such as endosomes or lysosomes), and in certain specific organs/cellular compartments under pathological situations (such as cancer or inflammation) [11, 12]. The pH-sensitive

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