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Thermosensitive hydrogel loaded with chitosan-carbon nanotubes for near infrared light triggered drug delivery

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ABSTRACT

Controlled drug release with on demand is an important challenge for drug delivery. Near-infrared (NIR) light triggered drug delivery reflected the development of a significant strategy to control drug release based on photothermal effects. Herein, a sustained and controlled drug delivery system was developed based on a PCL–PEG–PCL thermosensitive hydrogel combined with chitosan-multiwalled carbon nanotubes for a near infrared light triggered drug delivery. Carbon nanotubes that incorporate hydrogel can enhance the sustained effect of drug delivery by a dual-stage release and allow drug delivery by controlling light irradiation. This in situ photothermal process was monitored by thermal imaging and the controlled drug delivery of doxorubicin was tracked in real-time by fluorescence imaging in vivo based on the fluorescence ability of the drug using nude mice as models. The results suggest that the photothermal effect of the carbon nanotubes can disrupt the structure of the hydrogel with a gel–sol transition, triggering the release of the drug from the sustained drug delivery system by NIR irradiation while responding on demand. The sustained and controlled drug delivery has the potential to implement the accurate administration of hydrogel-based drug delivery systems.

1. Introduction

Hydrogels are three-dimensional semi-solid polymer networks that retain a large amount of water or biological fluid with excellent hydrophility and biocompatibility. Because of their soft nature, excellent permeability and structural similarity to extracellular matrices, hydrogels can afford a platform for the transport of nutrients and the growth of cells with minimized damage to the biotissues [1,2]. Their unique characteristics endow them with an important role in biomedical applications, among which, hydrogel-based drug delivery systems have received considerable attention since they can yield local high dose drugs in pathological tissues and reduce adverse effects in normal tissues with local administration [3–5]. Although hydrogels can release a drug spatially and sustainably by passive diffusion or hydrogel degradation, they still cannot satisfy the clinical requirements of spatial and temporal drug delivery on demand [6,7]. Sustained and controlled drug delivery is a focus when implementing accurate administration for hydrogel-based drug delivery systems.

The hydrogels combined with nanomaterials drug delivery systems can avoid the burst release of the hydrogels by a two stage delivery from the hydrogels and nanomaterials [8–10]. Nanomaterials including nanorods, nanoparticles and nanotubes have been widely applied in drug delivery systems with the development of nanomedicine and material sciences. Nano-drug carriers can effectively enhance the cellular uptake and bioavailability, reduce the adverse side effects and improve the therapeutic effects due to their special structure and properties [11]. However, the fast flexibility and rapid phagocytosis of the nano-delivery system could evoke the considerable drawback of lowering the therapeutic effect in local administration. To enrich the drug content of the local site and extend the drug duration, the nanocarrier combined with the hydrogel can enhance the strong points of both carriers and avoid the weaknesses of a single carrier. The dual drug delivery systems based on the nanocarrier combined with hydrogels have achieved obvious advances [12–14]. Two stages of drug delivery systems demonstrate their unique advantage for sustained drug delivery.

Controlled drug release on demand is another key issue that the hydrogel based drug delivery system must improve. Environmentally sensitive hydrogel can control the drug release in response to diverse stimuli, such as light, ultrasound, magnetic fields, elec-

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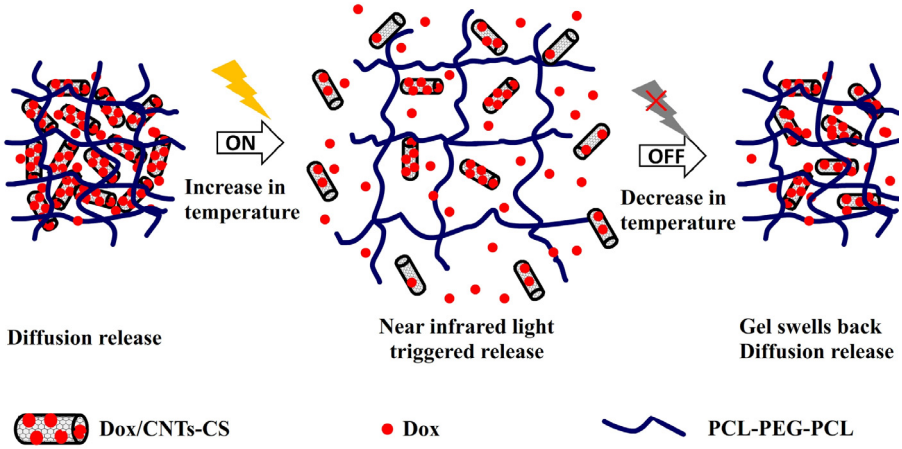

Fig. 1. Schematic of the near infrared light triggered drug delivery based on thermosensitive hydrogel loaded with chitosan-carbon.

tronic fields, pH and enzymes. The structural disruption of the hydrogel was triggered by the stimulating signal, leading to the controlled release of the entrapped drug [6]. Noticeably, light-responsive hydrogels attractive great interest for drug delivery over other stimuli for controlling the disruption of the hydrogel because of their advantages of non-invasive, controlled, remote and instant delivery [15,16]. However, traditional light-responsive hydrogels with UV or visible light irradition could suffer some drawbacks because of their limitation of penetration depth into tissue and the detrimental side effects to normal tissue from the high-energy irradiation. An alternative strategy to overcome these problems is the use of the near-infrared (NIR) light response hydrogel to control the drug delivery [17,18]. NIR absorbing nanomaterials that incorporate thermoresponsive hydrogel impact on an innovative direction for a controlled drug delivery system by photothermal effects, in which the structure of the thermoresponsive hydrogel was disrupted with a gel–sol transition by converting NIR light to heat [19,20]. Once the NIR irradiation is turned off, the drug release will be restrained with the structural recovery of the hydrogel from the disappearance of the heating effect. The photothermal hydrogel based drug delivery system has achieved great progress for on-demand drug delivery by the "on-off" adjustment from the photothermal effects of the NIR absorbing nanomaterials, including gold nanoparticles, carbon nanotubes and graphene oxide nanoparticles [21,22].

The combination of sustained release and controlled release is an ideal goal for accurate drug delivery via hydrogel-based drug delivery systems. Carbon nanotubes-thermoresponsive hydrogels explore a new strategy for achieving spatial and temporal drug delivery with the synergistic effect of sustained and controlled release. As potential delivery carriers, carbon nanotubes can improve the efficacy of therapeutic drugs by increasing their bioavailability and reducing their adverse side effect because of their effective permeation ability and strong loading capacity, which arise from their unique structural dimensions and chemical properties [23–25]. Carbon nanotubes incorporated into the hydrogel can obviously enhance the sustained effect of the drug delivery by a dual-stage release. Moreover, carbon nanotubes also control the structural transition of the hydrogel due to their strong photothermal effects for NIR light, allowing the on-demand drug delivery by the control of the light irradiation [26,27]. Carbon nanotubes-thermoresponsive hydrogels offer a unique advantage for drug delivery [14,28].

Herein, a sustained and controlled drug delivery system was developed based on the PCL–PEG–PCL thermosensitive hydrogel loaded with chitosan-multiwalled carbon nanotubes for near infrared light triggered drug delivery (Fig. 1). PCL–PEG–PCL thermosensitive hydrogel as a potential carrier has been widely applied in drug delivery systems in recent years [29]. Chitosan functionalized multiwalled carbon nanotubes can improve the dispersion and lower the toxicity of multiwalled carbon nanotubes in biological systems, thus enhancing the delivery efficiency of the drug carrier [26,30]. Doxorubicin (Dox), an anti-tumor drug, was loaded on functionalized multiwalled carbon nanotubes, and was then entrapped into the thermosensitive hydrogel to prepare the drug delivery system. Furthermore, the controlled drug delivery of Dox was real-time tracked by fluorescence imaging in vivo using nude mice as models based on the fluorescence ability of the drug. Owing to their special sustained and controlled ability, carbon nanotubes-hydrogel complexes maybe a potential candidate for an on demand drug delivery system.

2. Experimental

2.1. Materials

Poly(ethylene glycol) (PEG, Mn = 1000) was purchased from Merck & Co., Inc. (Germany) which was vacuum-dried at 60 °C for 12 h before use. ε-Caprolactone (ε-CL) and Stannous octoate ($Sn(Oct)_2$) were obtained from Aladdin Industrial Corporation (Shanghai, China), and ε-CL was purified by vacuum distillation. Doxorubicin hydrochloride (Dox) was purchased from Dakub Meilun Biology Technology Co., Ltd. (Dalian, China). Carbon nanotubes (CNTs) were purchased from DK Nano Technology Co., Ltd. (Beijing, China). Chitosan (CS) was provided by Haidebei Marine Bioengineering Co. Ltd. (Jinan, China). Chloral hydrate (>99.0, pharmaceutical grade) was purchased from Yulong Algae Co., Ltd. (Qingdao, China). Other reagents were all analytical reagent (AR) grade.

Balb/c nude mice (seven weeks old, 20–25 g) were used. All animal procedures were conducted following the protocol approved by the Institutional Laboratory Animal Ethics Committee, and all animal experiments were performed in compliance with the Guiding Principles for the Care and Use of Laboratory Animals, Peking Union Medical College, People's Republic of China. The animals were housed in cages with free access to food and water.

2.2. Preparation of Dox loaded CNTs/PCL–PEG–PCL hydrogel

First, Dox was loaded on the CNTs with non-covalent bonds. Dox (1 mg) was added into the black suspension with ultrasonic for 30 min and stirred for 16 h at room temperature after the CNTs