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Surface charge switchable and pH-responsive chitosan/polymer core-shell composite nanoparticles for drug delivery application

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ABSTRACT

The mutually conflicting surface charge requirements for nanoparticles to have long circulation and good cell affinity have made the development of polymer nanoparticles for controlled drug delivery fall into a dilemma. In order to solve this problem, the first attempt has been made in this work to develop vancomycin loaded composite nanoparticles with a novel chitosan core and poly (lactide-*co*-glycolide) (PLGA) shell structure and with both pH-responsive and surface charge switchable properties. Spherical composite nanoparticles have been successfully fabricated through a modified emulsion-gelation method with a controllable size (316–573 nm), surface charge (−27.6–31.75 mV) and encapsulation efficiency up to 70.8%. The dilemma can be avoided by tailoring the composite nanoparticles with the specially designed core-shell structure to be negative charged in the beginning and switch to positive charge later on. The negative charge of particles can be switched to positive charge gradually as the erosion of biodegradable polymer shells and exposure of the positive charged chitosan core. The formed chitosan hydrogel exhibited multi-layer structures, which were primarily influenced by chitosan concentration. Influences of the chitosan gelation behaviors on the properties of the composite nanoparticles in response to different chitosan and NH_3 concentrations have also been studied. Release rate decreased significantly with increasing chitosan concentration. With the introduction of the chitosan, the increase in drug release rate by orders of magnitude was observed for the samples immersing in the phosphate buffer saline solution of lower pH value proving a pH responsive release property. Drug release profiles of the composite nanoparticles were divided into fast release stage and slow release stage. The fast release stage was well described by a modified first-order kinetic model; while the slow release stage was fitted well with the classical first-order release kinetic model. All the presented results make the proposed composite nanoparticles a promising system for controlled drug delivery.

1. Introduction

Polymer nanoparticles with targeting capability have been widely developed as promising drug delivery vehicles [1–3]. Enhanced disease tissue accumulation and cellar internalization are two basic properties for nanoparticles to have achieved target delivery [4–6]. Tumor accumulation is usually achieved through a long circulation time and the permeability and retention (EPR) effect, which allows nanoparticles to penetrate through the leaky tumor vasculature other than normal tissue in a passive way [7,8]. Cellular internalization is another important step for the accumulated nanoparticles to have efficacious therapeutic results, which is associated with the size and surface properties of nanoparticles [9]. The internalization process is usually enhanced by grafting targeting ligands or the positive charged surfaces of nanoparticles, since these decorations on the particle surfaces can induce the ligand-receptor interactions or electrostatic interactions with cell membranes [10]. It has been discovered that positive charged or ligand decorated nanoparticles are generally easy to be recognized and cleared by the reticuloendothelial system (RES), which can significantly reduce the circulation time and thus deteriorate the accumulation of nanoparticles on tumor sites [11]. Prolonged circulation time and enhanced accumulation can be achieved by adopting

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negatively charged nanoparticles modified with hydrophilic groups, such as PEG, on their surfaces [12]. However, the negative charge and hydrophilic groups could hinder the interactions between nanoparticles and cell membrane, which is unfavorable for cellular interaction [13].

In order to solve this dilemma, nanoparticles with switchable surface properties are desirable. Nanoparticles are required to exhibit a negative charge before reaching tumor sites. After their accumulation on the tumor tissues, the nanoparticles are required to become positively charged in order to accelerate the cellular internalization. To realize this delivery strategy, some attempts have been employed to develop surface charge-switchable nanoparticles [7]. Hung et al. [14] developed a pH-triggered surface charge-switchable poly (lactide-*co*-glycolide) (PLGA) nanoparticles for drug delivery by grafting pH-responsive N-acetyl histidine modified D-α-tocopheryl polyethylene glycol succinate chains on the surface of the PLGA nanoparticles. These modified PLGA nanoparticles changed to be positively charged after being triggered by acid tumor extracellular environment due to the enhanced protonation of the grafted functional groups. In another study, negatively charged 2, 3-dimethylmaleic anhydride (DMMA) groups were introduced to shield the positively charged nanoparticles by binding them with the amino groups on the particle surfaces [15]. The DMMA groups detached from the amino groups responding to the tumor extracellular acidity would recover to become positively charged. Another strategy to achieve surface charge switching is the adoption of the Zwitterionic surfaces [16–18]. A variety of pH-responsive zwitterionic groups have been developed for the surface modification of nanoparticles, such as carboxybetaine [16], phosphorylcholine [17] and alkoxyphenyl acylsulfonaminde [18]. These functional groups are capable to switch from negative or neutral charges to positive charges at acidic environments. Thus, this type of surface modification has been proved to be an effective route to equip nanoparticles with a surface charge switching property. However, these surface modification processes are usually complex and may deteriorate the nanoparticles in certain extend.

PLGA, an American food and drug administration (FDA) approved polymer, has attracted increasing attentions as the primary composition of nanoparticles for drug delivery purpose, because of its degradability and controllable drug release profile [1,8,19–21]. However, the negatively charged surfaces of PLGA based nanoparticles render them inappropriate to have effective targeting effects. Chitosan, a natural occurring biodegradable polymer acquired from the deacetylation of chitin, has been widely adopted in industrial and pharmaceutical applications, because of its intrinsic properties such as biocompatibility, biodegradability, bacteriostatic effect and abundance in nature [1,22–25]. The positive charges of chitosan based nanoparticles are beneficial for cell affinity and internalization. However, the circulation time is compromised.

In this study, with motivation by the merits of both polymers, we have designed a novel and facile strategy for fabricating effective pH-responsive and switchable surface charged chitosan hydrogel/PLGA core-shell composite nanoparticles for drug delivery. A model drug, vancomycin HCl, was incorporated into the pH-responsive chitosan hydrogel core which was then encapsulated by the PLGA shell through a one-step emulsion gelation method. With the developed core-shell structure, the positively charged chitosan could be physically shielded. Following the erosion of the polymer shell and the exposure of chitosan core, the surface properties of the composite nanoparticles were switched from negative to positive charges. Gelation behaviors of the chitosan solution in response to the concentration of chitosan and alkali were studied. Influences of key fabrication parameters on the particle size, drug encapsulation efficiency, surface charge and drug release kinetics of the composite nanoparticles were all investigated.

2. Material and methods

2.1. Materials

Poly (lactic-*co*-glycolic acid) (PLGA) (Mw: ~30 kDa) and Poly ((D, L-lactic acid-*co*-glycolic acid)-block-ethylene glycol) (PLGA-PEG) (Mw: ~11 kDa) were obtained from the Jinan Daigang Biomaterial Co., Ltd. Dichloromethane (DCM), acetate acid and NH_3 solution were purchased from the Merck & Co. Polyvinyl alcohol (Mw: ~23 kDa) and tetraethylorthosilicate (TEOS) were acquired from the Sigma-Aldrich. Vancomycin HCl (VCM) was obtained from the Amresco. Chitosan (Mw = ~500 kDa, deacetylation degree, > 95%) was purchased from the Heifei Bomei Biotechnology Co., Ltd.

2.2. Fabrication of drug loaded chitosan/PLGA composite nanoparticles

The proposed composite nanoparticles were prepared through a modified gelation emulsion method [26]. Briefly, 30 mg of VCM was dissolved into 1 ml of chitosan solution. Chitosan solutions of different concentration (0.5%–2%) were prepared by dissolving the chitosan powder into acetate acid aqueous solution of the same concentration. 1 ml of the chitosan-VCM solution and 0.1 ml of NH_3 solution were ultrasonically emulsified into 5 ml of PLGA/DCM solution separately to form two emulsions. The PLGA/DCM solution was prepared by dissolving PLGA and PEG-PLGA with a weight ratio of 3: 2 into 5 ml of DCM. Both of the emulsions were blended and sonicated for 3 min to give a primary emulsion. The primary emulsion was then ultrasonically dispersed into 22 mL of 0.5% PVA solution to form the secondary emulsion which was then agitated for 3 h to evaporate all the organic solvent. The nanoparticle suspension was centrifuged at 12000 rpm for 30 min. The supernatants were kept for drug concentration analysis. The composite nanoparticles were obtained after washing and drying the precipitated solids.

2.3. Characterization

The morphologies and structures of the composite nanoparticles were examined using scanning electron microscopy (SEM) (JEOL JSM-6490) and STEM (JEOL JEM-2100F). Specimens for SEM were treated by coating a gold layer. Compositional information on the nanoparticles was obtained by Fourier Transform Infrared (FTIR) spectrometry (Thermo Scientific Nicolet IS50). The size and zeta potential of the nanoparticles were measured by a Zetasizer Nano ZS (Malvern Instruments, Malvern, U.K.) instrument.

2.4. Determination of encapsulation efficiency

The concentration of VCM in the supernatant was identified by measuring its absorbance using the UV spectrophotometry at 280.5 nm. A standard curve, that was used to calibrate the relationship between the drug concentration and UV absorbance, was prepared using a drug concentration of 0.6–0.032 mg/ml in 0.5% of PVA. The standard curve of drug concentration in response to UV absorbance was determined to be $y = 0.16672x\text{-}0.00421$ with a correlation factor R^2 of 0.999 in regression analysis. The encapsulation efficiency (EE) of the vancomycin in the nanoparticles was determined by identifying the concentration of the non-encapsulated free drug in the supernatant after centrifugation of the nanoparticle suspension at 12000 rpm for 30 min. The EE of the

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