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Preparation of injectable hydrogels from temperature and pH responsive grafted chitosan with tuned gelation temperature suitable for tumor acidic environment

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ABSTRACT

In this present work, stimuli responsive polymers that can respond to the temperature and pH of the environment were prepared. A series of temperature responsive diblock copolymers based on poly(ethylene glycol) methyl ether (mPEG) and ε-caprolactone (CL) were synthesized. Subsequently, the diblock copolymers were grafted onto chitosan, a pH responsive biopolymer. These chitosan-*graft*-(mPEG-*block*-PCL) (chitosan-*g*-(mPEG-*b*-PCL)) graft copolymers were structurally characterized by ^{1}H NMR and FTIR and their sol-gel phase transitions were analyzed by the test tube inversion method as well as dynamic rheological measurements. These chitosan-*g*-(mPEG-*b*-PCL) graft copolymers demonstrated tunable temperature and pH responsive sol-gel phase transitions that correspond well with body temperature and pH of acidic tumor microenvironments. Gelation temperature (T_{gel}) decreased with increasing pH of the system, increasing PCL composition in the diblock copolymers, increasing solution concentration and decreasing grafting content of the diblock copolymers on chitosan. The graft copolymer hydrogels successfully showed the sustained release of both doxorubicin and curcumin for up to 2 weeks. The designed system was based on chitosan-*g*-(mPEG-*b*-PCL) graft copolymers, of which chitosan showed pH responsive properties and mPEG-*b*-PCL acted as a temperature sensitive moiety. In addition, mPEG and PCL are recognized as biocompatible polymers and chitosan has been engaged in various pharmaceutical research. Thus, this system could be considered an alternative choice for drug delivery applications.

1. Introduction

Stimuli responsive polymers can change their physical properties when they are exposed to specific environmental stimuli. Changes in physical properties, for example changes in solubility, volume swelling, surface energy (hydrophobic-hydrophilic inversions), *etc.*, occur when the polymers are stimulated above a critical point. Removing the stimuli causes these polymers to change their physical properties back to the original state (Hoffman et al., 2000; Kikuchi & Okano, 2002; Schmaljohann, 2006; Ward & Georgiou, 2011). The stimuli can be, for instance, temperature, pH, light, magnetic field, electric field, ionic strength, solvents, *etc.* (Qiu & Park, 2012; Zhou, Jiang, Cao, Li, & Chen, 2015). Among these stimuli, temperature and pH are the most utilized triggers as they are not only easily controlled parameters but also are usually involved in several enzymatic functions in humans as well as other living creatures.

Among phase transition phenomena, sol-gel phase transitions are a common characteristic of injectable hydrogels. Injectable hydrogel polymers are an alternative design to replace conventional biomaterial implants. This polymer system dissolves in solution or is liquid until it is injected through a capillary needle. At the target site, the injected polymer solution is triggered by a stimulus, such as temperature or pH, to become a semi-solid, gel-like material (Huynh, Nguyen, & Lee, 2011; Manokruang & Lee, 2013). This liquid to gel transition or sol-gel phase transition, combined with the loaded medication, makes these materials potentially useful in the field of advance drug delivery treatments. Such systems provide advantages for reducing pain during the treatment since no surgical implantation is required for transporting the loaded drugs into the body. Compared to injectable hydrogels, administration of conventional drug-loaded hydrogels can cause pain during the implantation procedure. The release of active drugs from injectable hydrogels is comparable to regular treatments, but injectable hydrogels encapsulate the active drugs better than conventional hydrogels. Since the drug can be loaded in the hydrogel solution, drug loss is negligible

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Table 1
Preparation of the graft copolymers and their grafting contents.

copolymers[a]	mPEG45:CL (molar feed ratio)	$\overline{M}_n$ of mPEG-*b*-PCL[b]	Chitosan repeat unit:(mPEG-*b*-PCL) (molar feed ratio)	Grafting content[c] (%)
chitosan-*g*-(mPEG$_{45}$-*b*-PCL$_{13}$)	1:14	3484	1:0.5	5
chitosan-*g*-(mPEG$_{45}$-*b*-PCL$_{15}$)	1:17	3712	1:0.5	
chitosan-*g*-(mPEG$_{45}$-*b*-PCL$_{18}$)	1:19	4054	1:0.5	
chitosan-*g*-(mPEG$_{45}$-*b*-PCL$_{18}$)			1:1	7
chitosan-*g*-(mPEG$_{45}$-*b*-PCL$_{18}$)			1:2	10

Supporting information was provided for calculations of [a], [b] and [c].

when the whole system becomes gel immediately above the critical point. In addition, incorporating biodegradable polymers in the system not only helps to enhance its biocompatibility but also offers fast clearance of the materials through renal excretion (Gong, Shi, Dong et al., 2009; Gong, Shi, Wu et al., 2009; Zhao, Wu, Chen, & Xing, 2015).

Chitin and chitosan are polysaccharide biopolymers that are widely utilized in biomedical and pharmaceutical applications. Not only are they biocompatible but they also possess antibacterial activity (Kittur, Harish Prashanth, Udaya Sankar, & Tharanathan, 2002; Vandevord et al., 2002). The chemical structure of chitin is composed of 2-acetamido-2-deoxy-D-glucose subunits connected with β (1 → 4) linkages. Chitosan is obtained by N-deacetylation reaction of chitin with strong alkali at high temperature that converts the acetamido groups to amine groups. The extent of this conversion is called the degree of deacetylation (DD) of chitosan (Kasaai, 2010; Li et al., 2010). Although harvested from the same source, the properties of chitin and chitosan are different. Chitin is insoluble in water and most organic solvents but chitosan, due to its ionizable primary amine groups with a pKa of 6.3, is soluble in dilute acidic solutions with a pH lower than 6.0 (Yi et al., 2005). At low pH, the amine groups are protonated and become $-NH_3^+$, leading to strong electrostatic repulsion of the cationic charges. The open structure of the expanded chains allows for interactions with water and, as a result, this biopolymer is water-soluble. On the other hand, when the pH is higher than the pKa, amine groups are deprotonated and become $-NH_2$ with no charge. As a result, hydrophobic interactions and hydrogen bonding between the polymer molecules dominate, resulting in a globular collapsed structure and the exclusion of water. The polymer, then, becomes water insoluble. In addition, this pH responsive water-solubility of chitosan depends on DD and its pKa (Cho, Jang, Park, & Ko, 2000).

In this present work, injectable hydrogels that can respond to temperature and pH of the environment were prepared. A series of temperature responsive diblock copolymers based on poly(ethylene glycol) methyl ether (mPEG) and ε-caprolactone (CL) were synthesized. These diblock copolymers are temperature responsive polymers and their lower critical solution temperatures (LCST) are tunable based on the mPEG hydrophilic–CL hydrophobic balance (Gong, Shi, Dong et al., 2009; Gong, Shi, Wu et al., 2009). Subsequently, the diblock copolymers were grafted on chitosan, a pH responsive biomacromolecule. These chitosan-*g*-(mPEG-*b*-PCL) graft copolymers were structurally characterized by ^{1}H NMR and FTIR. Their sol-gel phase transitions were followed by the test tube inversion method as well as dynamic rheological measurements. Doxorubicin and curcumin were chosen respectively as hydrophilic and hydrophobic drug models to study the release from these injectable hydrogels.

2. Materials and methods

2.1. Materials

Poly(ethylene glycol) methyl ether (mPEG, Mn = 2000), succinic anhydride, anhydrous 1-hydroxybenzotriazole (HOBt) and stannous octoate (Sn(Oct)$_2$) were purchased from Sigma-Aldrich Co. Chitosan ($\overline{M}_n$ ≈200,000 and degree of deacetylation = 92%) was purchased from Seafresh Chitosan (Lab) Company Limited. 1-ethyl-3-(3-dimethylaminopropyl carbodiimide) (EDC) and ε-caprolactone (CL) were purchased from Acros Organics. All other chemicals and reagents were analytical grade.

2.2. Synthesis of mPEG-b-PCL diblock copolymers

Following well established procedures (Choi et al., 2005; Gong, Shi, Dong et al., 2009; Kim, Seo, Khang, Cho, & Lee, 2004; Xiong, Peng, Chen, & Li, 2015), mPEG-*b*-PCL diblock copolymers, with varying PCL block length, were synthesized by ring-opening polymerization in the presence of stannous octoate (1%mol equivalent to mPEG). For example, mPEG (13.0000 g, 6.5 mmol) was added to a dry round bottom flask and placed in an oil bath at 100 °C for 2 h to remove moisture from mPEG. To the flask, CL (10.3867 g, 91 mmol) was added and, then polymerization was carried out at 140 °C for 24 h under nitrogen atmosphere. The resulting diblock copolymer, mPEG$_{45}$-*b*-PCL$_{13}$, was precipitated in cold diethyl ether and was dried under vacuum. The other diblock copolymers, mPEG$_{45}$-*b*-PCL$_{15}$ and mPEG$_{45}$-*b*-PCL$_{18}$, were prepared by varying the molar feed ratios between mPEG and CL according to Table 1. The schematic representation of mPEG-*b*-PCL copolymer synthesis is shown in Scheme 1(A).

2.3. Synthesis of chitosan-g-(mPEG-b-PCL) graft copolymers

The diblock copolymers were modified to convert their terminal hydroxyl groups to carboxylic acids in the reaction as described in the published literature (Fangkangwanwong, Akashi, Kida, & Chirachanchai, 2006; Yoksan, Akashi, Hiwatari, & Chirachanchai, 2003). For example, mPEG$_{45}$-*b*-PCL$_{13}$ (20.9504 g, 6 mmol) was reacted with succinic anhydride (1.2012 g, 12 mmol) in 70 mL DMF. Excess succinic anhydride was used to ensure maximum conversion of all terminal hydroxyl groups to carboxyl terminated chains. The reaction was carried out at 60 °C for 24 h under nitrogen atmosphere. The carboxyl terminated mPEG$_{45}$-*b*-PCL$_{13}$-COOH was obtained by precipitating in 500 mL cold diethyl ether and was dried under vacuum prior to grafting onto chitosan. The reaction is schematically represented in Scheme 1(B). Preparation of the carboxyl terminated mPEG$_{45}$-*b*-PCL$_{15}$-COOH and mPEG$_{45}$-*b*-PCL$_{18}$-COOH were carried out *via* the same procedure.

In the grafting reaction, chitosan (0.2825 g, 1.73 mmol of chitosan repeat units) was stirred with HOBt (0.4682 g, 3.46 mmol) in a flask containing 20 mL deionized water. The emulsion of carboxyl terminated mPEG$_{45}$-*b*-PCL$_{13}$-COOH (3.0150 g, 0.86 mmol) containing EDC·HCl (0.6640 g, 3.46 mmol) in 15 mL deionized water was added into the flask. The reaction proceeded at room temperature for 48 h in a heterogeneous mixture where the diblock copolymers formed an emulsion in the solution of chitosan and HOBt, as schematically shown in Scheme 1(C). The product, chitosan-*g*-(mPEG$_{45}$-*b*-PCL$_{13}$), was obtained by precipitating into acetone and washed with a mixture of acetone and ethanol several times before it was dried in a vacuum oven. The other graft copolymers, chitosan-*g*-(mPEG$_{45}$-*b*-PCL$_{15}$) and chitosan-*g*-(mPEG$_{45}$-*b*-PCL$_{18}$), were prepared in the same manner by varying the molar feed ratios between chitosan repeat units and the diblock copolymers as detailed in Table 1. The concentrations of HOBt and EDC·HCl were kept constant at 2 M equivalents of chitosan repeat unit.

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