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Novel pH-sensitive chitosan-based hydrogel for encapsulating poorly water-soluble drugs

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ABSTRACT

Carboxymethyl–hexanoyl chitosan (CHC) is an amphiphilic chitosan derivative with excellent swelling ability and water solubility under natural conditions. In this work, the influence of the degree of carboxymethyl and hexanoyl substitution on the pH-sensitive swelling behavior, drug release behavior, and antiadhesion behavior of CHC hydrogels (cross-linked with genipin) were studied. It was found that the pH sensitivity was more pronounced in CHC than in N,O-carboxymethyl chitosan because the hexanoyl group altered the state of water in CHC by inhibiting intermolecular hydrogen bonding. In addition, greater pH sensitivity was observed in samples bearing longer hydrophobic chains (carboxymethyl–palmityl chitosan). Interestingly, when used with ibuprofen (a poorly water-soluble therapeutic agent used here as a model drug), the bursting release of the drug was less prominent in the CHC samples having a high degree of carboxymethyl substitution. The CHC hydrogel also demonstrated good cell compatibility and its antiadhesive ability after grafting was altered by changes in the degree of hexanoyl substitution.

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1. Introduction

In recent years, considerable attention has been focused on chitosan (CS) hydrogels and their use in tissue engineering scaffolds, controlled release and implants [1–3]. This is because of their glycosaminoglycan-like structure and wide range of outstanding characteristics such as biodegradability and availability. However, their application is limited by their poor water solubility under neutral physiological conditions, poor solubility in organic solvents, and lack of amphipathicity. Moreover, it is known that an increase in the hydrophobicity of a drug-loaded hydrogel, when administered via the mucosal route, will not only improve drug encapsulation efficiency but also drug transport across the buccal mucosa [4,5]. Therefore, several chitosan derivatives have been developed over the years with improved properties for enhanced applicability [6–8].

Recently, our group developed a novel chitosan derivative (carboxymethyl–hexanoyl chitosan, CHC) with excellent water solubility under neutral conditions [9]. In addition, we found that the presence of both carboxymethyl (hydrophilic) and hexanoyl (hydrophobic) groups affords an amphiphilic nature, which might make CHC suitable for use as a drug-loaded implant material for poorly water-soluble agents. In an earlier report, it was suggested that a CHC monolithic drug-loaded membrane could efficiently encapsulate ibuprofen (a nonsteroidal anti-inflammatory drug, IBU) which is poorly water soluble in the neutral physiological environment. In addition, recently, CHC micelles were also successfully prepared and employed for encapsulation of an antitumor agent with poor water solubility [10]. Moreover, it is expected that the CHC hydrogel might exhibit pH-sensitive behavior since it bears both acidic (COOH) and basic (NH_2) functional groups. The effects of the ionic functional groups on the nature of the pH response of chitosan derivatives have been described by several researchers [6,11]. However, little research has been done on the influence of hydrophobic substitution groups on this pH response. In our previous study, we performed preliminary investigations on the water absorption and water retention behavior of CHC [9]. However, it remains unclear whether the ligand substitutions influence the pH sensitivity of the resulting amphipathic hydrogel.

In general, the swelling (water absorption) behavior of pH-sensitive hydrogels is determined by the ionization of the functional groups of hydrogel and the intermolecular volume for water; the latter depends on the macromolecular structure, the state of water, the hydrophobic/hydrophilic characteristics, and the electric charge [12–14]. It is known that these factors also may govern cell adhesion to materials as well as drug release [15–17]. Hence, the influence of the hydrophobic substitution groups on the cell adhesion and drug release behaviors of the CHC hydrogel were also investigated in this study. The CHC hydrogel has a hyaluronan-like structure (Scheme 1) with controlled hydrophilicity/hydrophobicity and therefore has the potential to be employed as an

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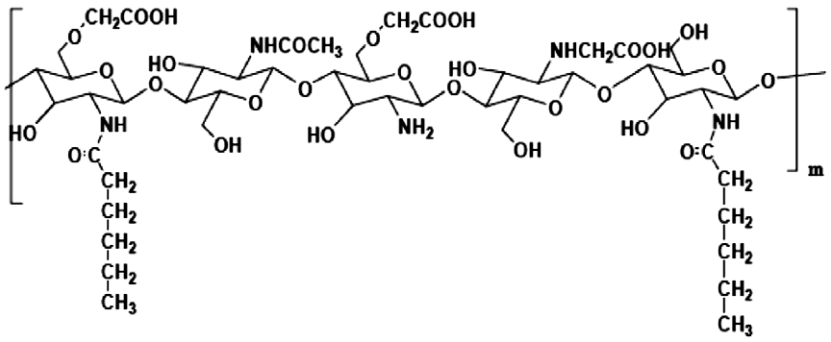


Scheme 1. Molecular structures of CHC.

ntiadhesive membrane encapsulating therapeutically active agents that prevent postoperative tissue adhesion.

The present study is focused on the influence of the degree of carboxymethyl and hexanoyl substitution on the pH-sensitive swelling behavior. In addition, IBU was employed as a poorly water-soluble model drug in order to investigate drug release behavior. Furthermore, a preliminary investigation of the variation in cytotoxicity and antiadhesive properties with the degree of hexanoyl substitution was also carried out.

2. Experimental

2.1. Materials

Chitosan (M_w = 215,000 g mol^{-1}, deacetylation degree = 80%, insoluble impurity < 1%), hexanoic anhydride, palmitic anhydride, and ibuprofen were purchased from Sigma–Aldrich. Genipin was sourced from WAKO. Methanol was purchased from TEDIA.

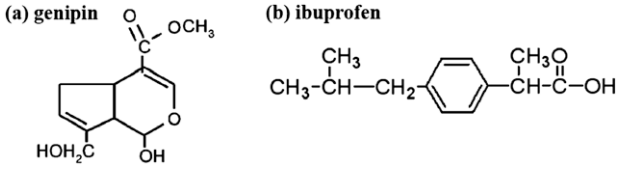
2.2. Synthesis of CHC and carboxymethyl–palmityl chitosan (CPC)

CHC was synthesized from N,O-carboxymethyl chitosan (NOCC). The synthesis of NOCC and CHC with various degrees of substitution has been reported in our previous work [9]. In brief, the home-made NOCC with low and high degrees of carboxymethyl substitution were named NOCC-1 and NOCC-2, respectively. The NOCC samples (2 g) were dissolved in distilled (DI) water (50 ml) and stirred for 24 h. The resulting solutions were mixed with methanol (50 ml), followed by the addition of hexanoic anhydride at concentrations of 0.3 M (low degree of hexanoyl substitution) and 0.5 M (high degree of hexanoyl substitution). CPC, an amphiphilic NOCC derivative bearing a longer hydrophobic chain, was produced by using palmitic anhydride instead of hexanoyl anhydride. After a reaction time of 12 h, the resulting solutions were dialyzed against an ethanol solution (25% v/v) for 24 h. The obtained ethanol/water-soluble (volume ratio = 3:2) chitosan derivatives with various degrees of carboxymethyl, hexanoyl, and palmityl substitution were named as shown in Table 1. For the subsequent material characterization, a 1.3% (w/v) solution of each chitosan derivative was prepared by dissolving the obtained derivatives in DI water. In order to prepare hydrogels, these solutions were then cross-linked with genipin solution (1% w/v; molecular structure shown in Scheme 2a) at 50 °C for 2 days [18]. The molar ratio of genipin to chitosan derivative was fixed at 300 for all samples to obtain the hydrogels with identical cross-linking density (i.e. effective number of cross-links per unit volume) rather than identical cross-linking degree (i.e. effective number of cross-links/total number of the D-glucosamine residues available for cross-link), which means that the influence of the retractile force on the swelling behavior was almost equal for each derivative. This is beneficial to enhance and clarify the influences of carboxymethyl and hexanoyl groups on the pH-sensitive swelling ratios and drug release behaviors of the CHC hydrogels.

Table 1
Estimated substitution degree (by ^{1}H NMR) for each sample.

	Carboxymethyl group	Hexanoyl group	D-Glucosamine residue
Degree of substitution			
NOCC-1	0.32	0	0.75
CHC-1A	0.32	0.26	0.49
CHC-1B	0.32	0.46	0.29
NOCC-2	0.50	0	0.73
CHC-2A	0.50	0.26	0.47
CHC-2B	0.50	0.48	0.25
		Palmityl group	
CPC	0.50	0.40	0.33

Degree of N-acetyl-D-glucosamine for all samples was around 0.2.



Scheme 2. Molecular structures of (a) genipin and (b) ibuprofen.

2.3. Material characterization

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded by an NMR spectrometer (Varian UNITYINOVA 500) at 270 MHz to confirm the degree of substitution. Attenuated total reflectance–Fourier transform infrared (ATR–FTIR) spectra were recorded on a spectrometer (Bomem DA8.3, Canada) using a film-type sample (4 cm × 0.5 cm). The ATR–FTIR spectra were recorded at a resolution of 2 cm^{-1} in the range 4000–400 cm^{-1}. The state of water was characterized by differential scanning calorimetry (DSC; Perkin-Elmer Instruments) [19]. Each dried sample was weighed in an aluminum pan to which different amounts of DI water were then added. Prior to the DSC test, samples with various water absorption ratios (W_C; $W_C = W_w/W_d$, where W_w and W_d are the weights of the moist and dry samples, respectively) were quenched from room temperature to −60 °C and conditioned at the same temperature for 10 min. The DSC curves were then obtained by reheating to 300 K at a scanning rate of 10 K min^{-1}.

2.4. Characterization of the swelling ratio

The samples for the swelling test were dried in a vacuum chamber with P_2O_5 for 24 h prior to the experiment. The test was

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