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ScienceDirect
Carbohydrate Research 342 (2007) 2416–2422
Carbohydrate RESEARCH

Preparation and properties of a pH/temperature-responsive carboxymethyl chitosan/poly(*N*-isopropylacrylamide)semi-IPN hydrogel for oral delivery of drugs

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Received 13 May 2007; received in revised form 3 July 2007; accepted 11 July 2007
Available online 18 July 2007

Abstract—Thermo- and pH-responsive semi-IPN polyampholyte hydrogels were prepared by using carboxymethylchitosan and poly(*N*-isopropylacrylamide) with *N*,*N*′-methylenebisacrylamide (BIS) as the crosslinking agent. The swelling characteristics of these hydrogels at distinct compositions as a function of pH and temperature were investigated. It was found that the semi-IPN hydrogels demonstrated the pH- and temperature-responsive nature of the materials, and it also showed good reversibility. The study on the release of coenzyme A (CoA) showed that within 24 h the cumulative release ratio of CoA was 22.6% in pH 2.1 solution and 89.1% in pH 7.4 solution at 37 °C, respectively. The release rate of CoA was higher at 37 °C than 25 °C in a pH 7.4 buffer solution. An increased release rate of CoA was observed with the content of carboxymethylchitosan increasing in the hydrogel at 25 °C in pH 7.4 solution. These results show that semi-IPN hydrogel seems to be of great promise in pH–temperature oral drug delivery systems.

Keywords: Biomaterials; Carboxymethylchitosan; Drug delivery systems; pH–temperature-responsive polymer; Semi-IPN polyampholyte hydrogel

1. Introduction

Amphoteric polyelectrolyte hydrogels possessing both positive and negative charges are interesting synthetic analogs for proteins. It is known that materials undergoing continuous or discontinuous volume phase transition responses to solvent composition,[1] pH,[2] salt concentration,[3] temperature,[4] and ultraviolet light[5] have received much attention recently because of their scientific and technological importance.[6–8] Among these systems, pH- or temperature-responsive hydrogels have been extensively studied in the biomedical field because these two factors can be easily controlled and are applicable both in vitro and in vivo conditions.[9–12]

It is known that the oral route is the most convenient and comfortable way of administering drugs. Successful oral drug delivery requires that the drug carrier is resistant both to attack by enzymes and to the impact of pH gradients (changing from pH 1–3 in the stomach to pH 6–7 in the intestine) for the gastrointestinal transit time from mouth to caecum (3–16 h) depending on the state of the stomach.[13] Therefore, resistance to acid and enzyme and time-controlled release are necessary for a viable oral drug carrier.

Carboxymethylchitosan (CM-CS), a natural amphoteric polyelectrolyte derived from chitosan has attracted considerable interest in a wide range of biomedical applications, such as wound dressings, artificial bone and skin, bacteriostatic agents, and blood anticoagulants, due to its unique chemical, physical, and biological properties, especially its excellent biocompatibility.[14–16] It has also demonstrated good pH and ion sensitivity in aqueous solutions due to abundant –COOH and $–NH_2$ groups.[17] The high degree of substitution of CM-CS hydrogels will swell significantly in basic solutions and will shrink dramatically in solutions of low-pH. So it is suitable to use as an oral delivery system for drugs.[18]

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0008-6215/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.carres.2007.07.007

Poly(*N*-isopropylacrylamide) (PNIPAm) is a widely studied temperature-sensitive polymer because it has a lower critical solution temperature (LCST) in the range of 30–32 °C, which is near that of the human body (37 °C).[19–21] This thermosensitive polymer has been made for gels[22] and beads,[23] and it has been extensively used as drug delivery systems, bioactive molecule separations,[24] and catalysts.[25] The copolymer of NIPAm with other functional monomers was widely used in the fields of chemistry, materials, and biotechnology.[26]

To combine the advantages of synthetic and natural polymers and at the same time maintain the favorable properties of natural polymers such as biodegradation and bioactivity, amphoteric polyelectrolyte hydrogels with pH- and temperature-sensitivity were synthesized with CM-CS and PNIPAm in this work. The swelling behavior of the semi-IPN hydrogel under different pHs and temperatures was studied. Coenzyme A (CoA) is widely used in the medical area. It can modulate the metabolism of sugar, fat, and protein in the body. It contains $–NH_2$, $–H_2PO_4$, –SH, and –NHCO ionic or polar groups. So the interaction of CoA and the polymer by H-bond or ionic complex occurs easily. CoA is readily soluble in water. In addition, the UV absorbance of CoA takes place at 260 nm, so it is very convenient to monitor it in solution by UV spectroscopy. The release behavior of CoA from the semi-IPN hydrogel was also investigated in simulated gastric and intestinal media in this paper. The results suggest that the hydrogel has great potential in the use of oral drug delivery systems.

2. Experimental

2.1. Materials

Chitosan (CS) was purchased from Tokyo Kasei Kogyo CO., Ltd. The degree of deacetylation (DA) was 0.85 as measured by elemental analysis.[27] Carboxymethylchitosan with 1.08 degree of substitution (DS) as determined by potentiometric titration[28] was prepared according to the literature method.[18] PNIPAm and coenzyme A (CoA) were all purchased from Aldrich Chemical Co. *N*,*N*′-Methylenebisacrylamide (BIS) for use as a cross-linking agent was purchased from Shanghai Reagent Corporation. Ammonium persulfate (APS) was obtained from Peking Chemical Industry, China, and recrystallized before use. All other chemicals were of analytical grade, used without further purification.

2.2. Preparation of CM-CS/PNIPAm semi-IPN hydrogels

Various ratios of NIPAm, CM-CS, and 5 wt % BIS based on the total monomers were dissolved in 6 mL of deionized water as described in Table 1. After bubbling N_2 gas for 30 min to deoxygenate the solution, 1 wt % APS as a redox initiator was added to the solution. Then the mixture was incubated at 40 °C for 24 h. After the gelation was completed, the semi-IPN hydrogel was cut into disks and immersed in an excess amount of deionized water for 4 days to remove the residual unreacted monomers. Swollen semi-IPN hydrogels were dried in a vacuum oven for 3 days at 30 °C to a constant weight. Then the dry hydrogel was weighed, and it was found that the dry hydrogel weight was almost equal to the materials (CM-CS, NIPAm, and BIS). The thickness of the dried hydrogel was about 1–1.5 mm, and the diameter of the particles was about 4–5 mm.

Drug-loaded semi-IPN hydrogel was prepared using a similar method for release experiments, in which CoA was mixed with the solution at a ratio of 10% (w/w) (relative to the total weights of CM-CS and NIPAm), and then gently stirred for 1 h at room temperature before APS was added into the mixed solution.

2.3. Characterization

IR spectra of the hydrogel were recorded using KBr pellets on an AVATAR-360 FTIR instrument at a resolution of 4 cm^{-1}. All the UV spectra of the release medium were recorded with a UV–vis spectrophotometer (UV-540, Vertex Instrument Corp., US).

2.4. Swelling studies

The swelling ratio (SR) was determined by immersing the dry semi-IPN hydrogels in aqueous solutions of the desired pH or temperature in sealed containers. After regular periods of time, they were removed from

Table 1. Feed composition for the preparation of semi-IPN hydrogels

Component	Sample code			
	PNIPAm	Semi-IPN05	Semi-IPN15	Semi-IPN30
NIPAm (g)	0.480	0.480	0.480	0.480
W (CM-CS) (%)[a]	0	5	15	30
m (BIS) (g)	0.0240	0.0240	0.0240	0.0240
m (APS) (g)	0.0048	0.0048	0.0048	0.0048
V (H_2O) (mL)	6	6	6	6

[a] The concentration is based on the mass of monomer NIPAm.