



Regular article

Design and evaluation of chitosan- β -cyclodextrin based thermosensitive hydrogel



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ABSTRACT

The thermosensitive hydrogel was prepared by embedding β -cyclodextrin into chitosan/ $\alpha\beta$ -glycerol phosphate system. The optimal parameters were that the ratio of CS/ β -CD was 2/1 (w/w) and the ratio of CS- β -CD/ $\alpha\beta$ -GP was 9.0/1.0 (v/v), where the gelation time was less than 3 min. The hydrogels had obvious lamellar structure, self-comparability, fractal characteristic and had good sustained release efficiency on the hydrophobic drug. Furthermore, the release rate of CS- β -CD-In hydrogel was slower than that of CS- β -CD hydrogel which indicated that the model drug (Asprin), added as Asp- β -CD inclusion, was beneficial for sustaining the release from the modified hydrogel system. The analysis of release kinetics indicated that both CS- β -CD based hydrogel and CS- β -CD-In hydrogel showed best fit with Peppas model and had potential as sustained release drug delivery system.

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1. Introduction

In the past few years, physical crosslinked hydrogel without organic crosslinking agents were attracting a great deal of interest in biomedical application including drug delivery, cell encapsulation, and tissue engineering [1–3]. Recently, one of the thermosensitive systems which could keep liquid at room temperature and form gel at body temperature under physiological condition had gained increasing attention [4,5]. Early research in the field focused on the synthetic materials of thermosensitive gel including poly(ethylene glycol)/poly(lactic acid-co-glycolic acid) block copolymers, poly(methyl vinyl ether-co-maleic anhydride) copolymers, poloxamer-g-poly(acrylic acid), and polymers of *N*-isopropylacrylamide that exhibited a sol-to-gel transition in aqueous solutions [6–9].

Chitosan was a natural cationic polysaccharide, normally obtained by partly deacetylation of chitin, which was composed of *N*-acetylglucosamine and glucosamine residues. Chitosan had

been examined and proposed as a biomaterial in the development of controlled and targeted release of drug delivery systems because of its biocompatibility, biodegradability and nontoxicity [4,10–12]. Glycerophosphate was an organic compound naturally found in the body which was usually used as a source of phosphate in the treatment of phosphate metabolism disturbances, as well as, its venous administration had been approved by food and drug administration (FDA). β -glycerophosphate had been shown as an osteogenic supplement when added to cultures of human bone marrow stem cells [13]. $\alpha\beta$ -glycerophosphate is a mixture of α -glycerophosphate and β -glycerophosphate, and α -glycerophosphate has linear chain structure and shows less steric hindrance than β -glycerophosphate. Glycerophosphate also had been used as a catalyst to cause a sol-to-gel transition in chitosan solutions at physiological pH and temperature. In previous study, we had developed chitosan/ $\alpha\beta$ -glycerophosphate thermosensitive hydrogel as a drug delivery carrier [14,15]. The results showed that the prepared hydrogel was liquid at room temperature and gels at 37 °C. Moreover, the prepared hydrogel showed a controlled release behaviour of adriamycin as a model drug [16,17].

However, the burst release and improving the solubility and bioavailability of hydrophobic drugs loaded were inescapably

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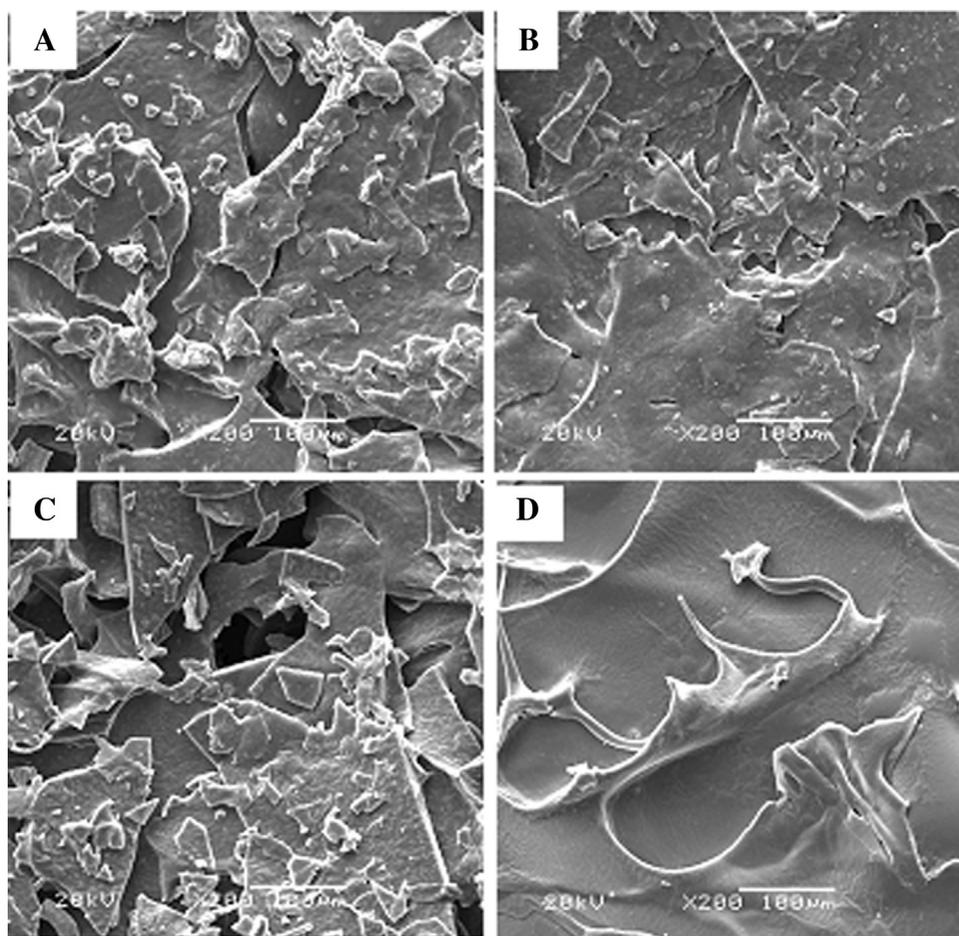


Fig. 1. SEMs of CS-β-CD hydrogel with different formulation.

A: CS/β-CD = 1/1 (w/w), CS-β-CD/αβ-GP = 9.0/1.0 (v/v);
 B: CS/β-CD = 1/1 (w/w), CS-β-CD/αβ-GP = 9.2/0.8 (v/v);
 C: CS/β-CD = 2/1 (w/w), CS-β-CD/αβ-GP = 9.0/1.0 (v/v);
 D: CS/β-CD = 4/1 (w/w), CS-β-CD/αβ-GP = 9.0/1.0 (v/v).

becoming a critical limitation of using the hydrogel as a drug delivery system. Therefore, it is urgently necessary exploiting new-type chitosan based hydrogel, not only with the excellent original properties of hydrogel, but also with the great ability to keep long-term sustained-release of drugs loaded. A new strategy was developed by loading a variety of different geometries and formulations such as liposomes, microspheres, vesicles and nanoparticles into thermosensitive hydrogel [18–21]. Recently, β-cyclodextrin inclusion complexes with hydrophobic drugs were embedded into such hydrogel in an attempt to improve the characteristics of these gels [22,23].

β-cyclodextrin was well known for the host-guest interaction which was a kind of cyclic oligosaccharide composed of seven units of (α-1, 4)-linked α-D-glucopyranose arranged in a truncated cone shape structure [24,25]. β-cyclodextrin was converted from starch through a process of cyclization catalyzed by cyclodextrin glycosyltransferase [26,27]. The hydrophilic outer surface and hydrophobic central cavity of β-cyclodextrin made it possible to accommodate a variety of hydrophobic drugs through hydrophobic interactions [28]. β-cyclodextrin inclusion played a significant role in improving the bioavailability, increasing the solubility, reducing the irritation, masking smell and affecting the release of active substances from the pharmaceutical system [29,30]. So it might be a useful approach to improve the characteristics of hydrogel by introduc-

ing the β-cyclodextrin inclusion into the chitosan hydrogel. Other similar formulations, which fabricated by adding β-cyclodextrin or HP-β-Cyclodextrin into chitosan/β-glycerophosphate hydrogel have been demonstrated to have good properties in terms of pH, gelation, viscosity and in-vitro release [22,23]. So the embedding of β-cyclodextrin into the chitosan/αβ-glycerophosphate hydrogel was essential to be evaluated.

Asp was the optimal drug in the treatment of rheumatic fever and rheumatic arthritis, was recommended for the primary and secondary prevention of diabetes mellitus and now commonly used in reducing the risk of arterial vascular events. However, Asp may cause damage to gastric mucosa and induce gastric bleeding because of the slightly higher acidity of the drug resulting from the presence of carboxy and the drug was slightly soluble in water and decomposed easily.

In this study, chitosan-β-cyclodextrin based injectable in situ thermosensitive hydrogel (CS-β-CD hydrogel) was prepared by adding β-cyclodextrin into the chitosan based system as sustained release delivery system. The effect of the ratio of chitosan to β-cyclodextrin (CS/β-CD, w/w) and chitosan-β-cyclodextrin solution to αβ-glycerophosphate solution (CS-β-CD/αβ-GP, v/v) on the characteristics and sol-to-gel transition of hydrogel were investigated. In addition, Aspirin (Asp; 2-acetyloxy benzoic acid) was selected as model drug. So Aspirin-β-cyclodextrin inclusion

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