Carbohydrate Polymers 83 (2011) 1507–1515

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Carboxymethylation of *kappa*-carrageenan for intestinal-targeted delivery of bioactive macromolecules

Kok Hoong Leong[a], Lip Yong Chung[a,*], Mohamed Ibrahim Noordin[a], Khalit Mohamad[a], Masato Nishikawa[b], Yoshinori Onuki[b], Mariko Morishita[b], Kozo Takayama[b]

[a] Department of Pharmacy, Faculty of Medicine, University of Malaya, Kuala Lumpur 50603, Malaysia
[b] Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Hoshi University, 2-4-41 Ebara, Shinagawa, Tokyo 142-8501, Japan

ARTICLE INFO

Article history:
Received 16 July 2010
Received in revised form
28 September 2010
Accepted 30 September 2010
Available online 7 October 2010

Keywords:
Carboxymethylation
Carrageenan
Microencapsulation
Drug delivery
Response surface methodology

ABSTRACT

The work presented herein discusses the carboxymethylation of *kappa*-carrageenan, a natural linear polysaccharide, to afford a pH-dependent swelling property allowing for intestinal-targeted delivery of bioactive macromolecules. The carboxymethylation conditions with respect to the volume and concentration of sodium hydroxide (V_{NaOH}, C_{NaOH}), weight of monochloroacetic acid (W_{MCA}), and reaction temperature (T) were optimized using a response surface method incorporating a multivariate spline interpolation technique (RSM^S). Fluorescein isothiocyanate-labeled dextran (FD-4; 4.4 kDa) was used as a hydrophilic macromolecule model. Beads made from encapsulating FD-4 in the carboxymethylated *kappa*-carrageenan displayed pH-dependent swelling and encapsulation efficiency of 74%. The release of FD-4 was low (23 ± 2%) in simulated gastric fluid (SGF) and high (90 ± 3%) in simulated intestinal fluid in a 2 h dissolution study. An additional *lambda*-carrageenan coating on the surface of the beads further reduced the FD-4 release in SGF. These carboxymethylated *kappa*-carrageenan beads may provide an efficient alternative approach for the oral delivery of hydrophilic macromolecules to the intestinal tract.

1. Introduction

Recent advances in biotechnology have driven the need to design suitable carriers for the oral delivery of bioactive macromolecules. Some bioactive macromolecules that have captured great interest include peptide or protein-based drugs, such as insulin and cyclosporine (Tan, Choong, & Dass, 2010); hormones such as thyrotropin-releasing and human growth hormone (Amet, Wang, & Shen, 2010; Tan et al., 2010); genes and vaccines for oral immunization (Chadwick, Kriegel, & Amiji, 2010; Page & Cudmore, 2001). However, there are critical barriers in creating an effective system for oral delivery of bioactive macromolecules, including low oral bioavailability due to their degradation in the highly acidic stomach environment, the presence of digestive enzymes, and the low permeability of these macromolecules through the intestinal epithelium (Chadwick et al., 2010; Page & Cudmore, 2001; Tan et al., 2010). Encapsulation of bioactive macromolecules improves their protection against degradation by low gastric pH and enzymes, providing a controlled release of the entrapped macromolecules (Tan et al., 2010). This encapsulation can be performed using natural polysaccharides such as alginate, chitosan and pectin (Liu, Jiao, Wang, Zhou, & Zhang, 2008).

Carrageenans are naturally occurring linear polysaccharides extracted from red seaweed. They have high molecular weight and are composed of repeating galactose residues. There are three primary classes of carrageenans available depending on the number and position of the ester sulfate groups, termed *kappa*-, *iota*-, and *lambda*-carrageenan. They have long been used commercially in the food industry, and now increasingly in pharmaceutical formulation studies (Gupta, Hariharan, Wheatley, & Price, 2001). They are known to form microparticles by *in situ* ionic gelation, and have successfully encapsulated some model drugs such as ibuprofen and verapamil (Sipahigil & Dortunc, 2001). Therefore, it is plausible that they could be used to encapsulate macromolecular drugs for oral delivery.

Although carrageenans are capable of encapsulating drugs, an efficient carrier for macromolecular drugs is required to ensure the release of its encapsulated drug in the intestinal region in order to prevent premature release and/or degradation in the stomach. Site-specific targeted release can be implemented by attaching pH-sensitive groups, such as carboxylic acid groups (–COOH), to the carrageenan polymeric structure through a carboxymethylation process. This pH-dependent swelling property is well suited for site-specific drug delivery to the intestine due to the change in pH from acidic (pH ~ 1.2) in the stomach to slightly alkaline (pH ~ 7.4) in the intestine as the drug carrier transits through the gastrointestinal tract (Peppas, Bures, Leobandung, & Ichikawa, 2000).

* Corresponding author. Tel.: +60 3 79674971; fax: +60 3 79674964.
E-mail addresses: chungly@um.edu.my, chungly@hotmail.com (L.Y. Chung).

0144-8617/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carbpol.2010.09.062