Lectin-functionalized carboxymethylated kappa-carrageenan microparticles for oral insulin delivery

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ABSTRACT

We hypothesized that pH-responsive carboxymethylated kappa-carrageenan microparticles could protect entrapped oral insulin from acidic and proteolytic degradation in the gastrointestinal tract. Therefore, the objectives of this study were to prepare and characterize insulin entrapped in lectin-functionalized carboxymethylated kappa-carrageenan microparticles and to evaluate their therapeutic efficacy in vitro and in vivo. The encapsulation of insulin was performed using an ionic gelation technique and was optimized to give an encapsulation efficiency of 942 ± 2.6% and a drug-loading capacity of 13.5 ± 0.4%. The microparticles were further surface-lectin-functionalized for improved intestinal mucoadhesiveness. The oral administration of insulin entrapped in the microparticles led to a prolonged duration of the hypoglycemic effect, up to 12–24 h, in diabetic rats. From the release profile and the low toxicity of the microparticles, it can be concluded that these lectin-functionalized carboxymethylated kappa-carrageenan microparticles have the potential to be developed into an oral insulin delivery system.

1. Introduction

The current administration of peptide-based drugs, such as insulin, is predominately via the parenteral route, which has a number of disadvantages. These include discomfort due to repeated and prolonged dosage regimes, high variation in bioavailability and a non-physiological delivery pattern (Takei & Kasatani, 2004). These issues have brought about an increased effort to develop alternative delivery systems (Pillai & Panchagnula, 2001). The recent introduction of an inhaled delivery system for insulin was short-lived and resulted in the withdrawal of the product from the market by pharmaceutical companies (Opav, 2008). Recently, a pre-clinical study of an oral insulin formulation for type-2 diabetic patients showed promising results (Kapitza et al., 2010). Therefore, the oral delivery of insulin still remains an attractive alternative delivery route. Some advantages of the oral delivery system include the elimination of the risk of needle infection, increased patient compliance and a lower cost of therapy (Heller; Kozlovi, & Kurtzhals, 2007; Russell-Jones, 2004). It is also more physiologically relevant because orally administered insulin undergoes first hepatic bypass and produces

a similar effect to pancreas-secreted insulin (Sarmiento, Ribeiro, Veiga, Ferreira, & Neufeld, 2007). However, peptide-based drugs, such as insulin, are difficult to deliver orally due to enzymatic degradation and their inability to transverse the biological barriers of the gastrointestinal tract. Therefore, recent research has focused on protecting the drug from degradation using drug carriers that include enzyme inhibitors and improving absorption via the incorporation of permeability enhancers (Khahag, Morishita, Onuki, & Takayama, 2007).

Among the drug carriers investigated, carriers derived from natural polysaccharides have commanded particular interest due to their biodegradability, biocompatibility, hydrophilicity and protective properties (Liu, Jiao, Wang, Zhou, & Zhang, 2008). Natural polysaccharides, such as alginites and chitosan, were extensively used because of their favorable characteristics for drug entrapment (Sarmiento, Ferreira, Jorgensen, & van de Weert, 2007). The advantage of using such hydrogels is the ease of performing water-based ionotropic gelation during the process of drug encapsulation. Moreover, it has been shown that ionotropic gelation preserves the bioactive conformation of the insulin drug (Martins, Sarmiento, Souto, & Ferreira, 2007).

A recent report shows that the incorporation of dectan sulfate in the encapsulation of insulin with alginate and chitosan polymer mixtures improved the protection of insulin in an acidic in vitro environment. The enhanced protection is attributed to the