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Novel mucoadhesion tests for polymers and polymer-coated particles to design optimal mucoadhesive drug delivery systems☆

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Abstract

To design an effective particulate drug delivery system having mucoadhesive function, several mucoadhesion tests for polymers and the resultant particulate systems were developed. Mucin particle method is a simple mucoadhesion test for polymers, in which the commercial mucin particles are used. By measuring the change in particle size or zeta potential of the mucin particle in a certain concentration of polymer solution, we could estimate the extent of their mucoadhesive property. BIACORE method is also a novel mucoadhesion test for polymers. On passing through the mucin suspension on the polymer-immobilized chip of BIACORE instrument, the interaction was quantitatively evaluated with the change in its response diagram. By using these mucoadhesion tests, we detected a strong mucoadhesive property of several types of chitosan and Carbopol.

Evaluation of mucoadhesive property of polymer-coated particulate systems was demonstrated with the particle counting method developed by us. To detect the mucoadhesive phenomena in the intestinal tract, we observed the rat intestine with the confocal laser scanning microscope (CLSM) after oral administration of the particulate systems. The resultant photographs clearly showed a longer retention of submicron-sized chitosan-coated liposomes (ssCS-Lip) in the intestinal tract than other liposomal particles tested such as non-coated liposomes and chitosan-coated multilamellar one. These observations explained well the superiority of the ssCS-Lip as drug carrier in oral administration of calcitonin in rats than other liposomal particles.

Keywords: Mucoadhesion; Mucin particle; BIACORE; Confocal laser scanning microscopy; Peptide drug; Oral administration

Contents

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1. Introduction

Colloidal drug carriers, such as liposomes or nanoparticles of biodegradable polymers, have received much attention for their ability to improve the absorption of poorly absorbable drugs, including peptide drugs. It has been reported that the mucoadhesive properties of these particulate systems can prolong their retention in the gastrointestinal tract, thus further improving drug absorption [1].

We have demonstrated a novel mucoadhesive liposomal system prepared by coating the liposome surface with a mucoadhesive polymer, chitosan. The effectiveness of the chitosan-coated liposomes (CS-Lip) was confirmed by the enhanced and prolonged pharmacological effect of insulin, which was orally administered in the polymer-coated liposomal form in rats [2,3]. The effectiveness of mucoadhesive liposomes in drug absorption was also demonstrated by using calcitonin as a model peptide drug. Carbopol-coated liposomes, having a mucoadhesive property similar to that of CS-Lip, were as effective as CS-Lip [4].

A particulate bioadhesive system was also prepared by coating microspheres of poly-hydroxyethyl-methacrylate with mucoadhesive polymers using laboratory-scale equipment [5,6]. Akiyama et al. [7] prepared a polyglycerol ester of fatty acid-based microspheres coated with Carbopol934P (CP) and CP-dispersing microspheres to evaluate their mucoadhesive properties. In developing colloidal drug delivery systems, Lenaerts et al. [8] demonstrated the mucoadhesive property of polyalkylcyanoacrylate nanoparticles with autoradiographic studies and confirmed that the bioavailability of vincamine was improved in nanoparticulate systems. Pimienta et al. [9] investigated the bioadhesion of hydroxypropylmethacrylate nanoparticles or isohexylcyanoacrylate nanocapsules, the latter coated with poloxamers and poloxamine on rat ileal segments in vitro using a labeled compound.

To design optimal mucoadhesive drug delivery systems such as polymer-coated liposomes, it is necessary to develop simple mucoadhesion tests that can evaluate the mucoadhesive properties of polymers. The development of mucoadhesion tests for particulate systems is also important.

The most direct method is to measure the bioadhesive bond strength between a polymer and the mucosal layer of animals [10]. Ch'ng et al. [11] demonstrated the feasibility of this concept by using a polymer specimen and freshly excised stomach tissue from an animal. Ponchel et al. [12] developed a similar method to measure tensile force. Smart et al. [13] proposed the use of the Wilhelmy plate method, which is usually applied to determine surface tension. A rheological method proposed by Hassan and Gallo [14] is an alternative way to assess mucin–polymer adhesive bond strength. They evaluated bioadhesion forces by monitoring viscometric changes in a mixture of porcine gastric mucin and polymers in solution.

In this paper we propose two types of novel mucoadhesion tests for polymers. We also report on tests we developed for mucoadhesive particulate systems.