Poly(acrylic acid)/Polyethylene Glycol Hygrogel Prepared by Using Gamma-ray Irradiation for Mucosa Adhesion

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I. INTRODUCTION

Controlled systems for drug delivery to mucosal surfaces, such as gastrointestinal, ocular, respiratory, buccal, nasal, and rectal vaginal path surface, have attracted wide interest around the world [1–3]. However, a viscoelastic and sticky mucus layer on all mucosal tissues has evolved to protect the body by rapidly removing foreign materials. Mucoadhesive polymers are utilized to immobilize a drug on a specific site for a targeted release and optimal drug delivery. Thus far, a considerable number of studies have been performed using hydrophilic polymers containing numerous hydrogen-bond forming groups, with a focus on the mucoadhesive properties of a wide range of polymeric materials. The interaction between the mucus and the mucoadhesive polymers has been proposed to be attributable to a physical entanglement and secondary bonding, mainly H-bonding and a van der Waals attraction, which are related to the chemical structure of the polymers. The surface chemical groups of mucoadhesive polymers that contribute to mucoadhesion include hydroxyl, carboxyl, amine and amide groups in the structure. Pepas et al. suggested that a polymer which had a mucoadhesion function would have the following characteristics: strong H-bonding groups, strong anionic charges, high molecular weight, sufficient chain flexibility, and surface-energy properties favoring a...
spread onto mucus [4].

Typical polymers used as mucoadhesive drug carriers include poly(acrylic acid) (PAA), poly(methacrylic acid) (PMA), carboxymethyl cellulose (CMC), modified chitosan, and hydroxypropyl methylecellulose [5–9]. Of these polymers, PAA and its crosslinked commercial powder forms, Carbopol and Polycarbophil, usually show strong mucoadhesive properties. Carbopol is a crosslinked PAA-based polymer that has excellent bioadhesive properties over the short term when formulated as an aqueous system. However, rapid hydration can occur, leading to a breakdown of the gel’s structure and finally adhesive failure. Also, PAA alone has limitations as a mucoadhesive drug carrier owing to its high water solubility, because of which it may be dissolved before the drug is delivered across the membrane. Many studies have been conducted to solve this problem by using copolymers, interpolymer complexes, or crosslinking [10–12].

Hydrogels are macromolecular networks that swell, but do not dissolve, in water. Hydrogels can be synthesized by accomplishing crosslinking through radiation [13–16]. For the fabrication of hydrogels, the gamma-ray irradiation technique has several advantages, such as easy process control, the possibility of combining hydrogel formation and sterilization into one technological step, no necessity to add any initiators, and a crosslinker [17–19]. However, UV irradiation method requires additional photoinitiators to induce the formation of free radicals. Most photoinitiators are toxic and difficult to remove from a polymer [20,21]. However, little work has been done on the mucoadhesion of hydrogels synthesized by irradiating of PAA or its copolymer solution.

The aim of the present study is to develop a suitable PAA-based mucoadhesive that might have a potential for localized prolonged delivery of active agents into an oral cavity. In this experiment, PAA and polyethylene glycol (PEG) were selected to prepare using a radiation process a bioadhesive hydrogel for adhesion to mucosal surfaces.

II. EXPERIMENTAL DETAILS

PAA with M.W. 100,000 that was purchased from Waco Pure Chemical Industries, Ltd (Osaka, Japan) was used without further purification. PEG with M.W. 10,000 was supplied by Sigma Aldrich (Missouri, USA) and was used without further purification.

In this experiment, hydrogels were prepared using PAA and PEG. PAA was dissolved in purified water to make a 7 wt% PAA solution, and 0.25 − 1 wt% of PEG was then incorporated into the PAA solution. Three ml of a homogenous solution were put into a 35 mm Petri dish and were then irradiated by using an electron beam accelerator (10 MeV/1 mA, Jeongup site of Korea Atomic Energy Research Institute, Junbuk, Korea) at dose up to 70 kGy to make the hydrogels.

The hydrogels prepared through irradiation were dried to measure the gelation. The dried hydrogels were extracted with water for 24 hr at room temperature to extract the insoluble part of the hydrogel. The insoluble part, i.e., the gelled part, was taken out and washed with water to remove the soluble part, and were then dried and weighed. This extraction cycle was repeated until the weight became constant. The gel percent in the hydrogel was determined from the following equation:

\[
\text{Degree of gelation (\%)} = \left( \frac{W_c}{W_d} \right) \times 100
\]

where \(W_d\) and \(W_c\) represent the weights of the dried hydrogel and the gelled part after extraction, respectively.

The dried hydrogels, which were punched into discs, were weighed and allowed to swell in distilled water. The degree of swelling at equilibrium was calculated as follows:

\[
\text{Swelling percent (\%)} = \left( \frac{W_s - W_d}{W_d} \right) \times 100
\]

where \(W_d\) and \(W_s\) represent the weights of the dry and the wet hydrogel, respectively.

The buccal mucosa from a pig was used to determine the mucoadhesive properties of the hydrophilic crosslinked PAA-based specimens. Hydrogels, 3 mm in thickness, were dried, cut into 10 mm diameter circles, and then fixed to a cylindrical probe (10 mm in diameter) by using double-sided adhesive tape (Fig. 1(a)). A buccal mucosa specimen of a pig was cut into size of 30 \(\times\) 30 mm\(^2\), and were fixed to the surface of a stainless steel plate. Peel testing of the sample film was carried out using a universal mechanical tester equipped with a mucoadhesive holder. Figure 1 shows the procedure for the mucoadhesive test. The probe with a PAA-based polymer disc was pulled out at a speed of 0.5 mm/sec after attachment to the mucosa’s surface at a contact force of 0.05 N for a contact time of 60 sec.

The other evaluation method of mucoadhesion in this experiment was examining the amount of time the adhesion was maintained between a PAA-based specimen and the buccal mucosa in phosphate buffered saline solution under stirring. Hydrogels, 3 mm in thickness, were