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COMMUNICATION

Mucoadhesive and Physicochemical Characterization of Carbopol-Poloxamer Gels Containing Triamcinolone Acetonide

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ABSTRACT

The viscosity and bioadhesive property of Carbopol-Poloxamer gels containing triamcinolone acetonide to mucosa were tested according to various concentrations of Carbopol gels of various pH. The increase in Carbopol concentration caused increased viscosity and bioadhesiveness. The neutralization of pH in various concentrations of Carbopol gels showed the increased viscosity, showing the highest viscosity and highest bioadhesiveness when neutralized to pH 6. A relationship between the viscosity and bioadhesive strength was shown from the neutralized Carbopol gels. The physicochemical interactions between triamcinolone acetonide and polymers were investigated by X-ray diffraction (XRD) and Fourier transform infrared (FTIR) spectrophotometry. According to FTIR and XRD studies, the drug did not show any evidence of an interaction with the polymers used and was present in an unchanged state.

Key Words: *Carbopol; Gels; Mucoadhesive; Poloxamer; Solid dispersion; Triamcinolone acetonide.*

INTRODUCTION

During the past few years, there has been increasing interest in the development of new formulations that can control the release of drugs through the mucosa using bioadhesive polymer. That is because this kind of form offers the prospects of prolonging the residence time of controlled-release systems at the sites of drug absorption and ensuring optimal contact between the formulation and the absorption site (1–3).

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In the case of oral application of the conventional dosage forms such as ointments, solutions, creams to buccal mucosa, it is difficult to maintain their effects for a significant period of time because they are very easily removed by salivation, temperature, tongue movement, and swallowing. We need to develop new formulations that have suitable bioadhesion or adhesive time and provide sustained release in the buccal area for an extended period of time. Bioadhesive gels containing triamcinolone acetonide were prepared using two polymers, such as Carbopol 934 and Poloxamer 407. The former was selected for its bioadhesiveness and the latter for its gelling property.

The Carbopol resins are very high molecular weight polymers of acrylic acid cross-linked with polyalkenyl ethers (4), and they have been used for development of bioadhesive controlled-release drug delivery systems owing to their bioadhesive properties. The Poloxamers, nonionic surface-active agents, are triblock copolymers consisting of polyoxyethylene-polyoxypropylene-polyoxyethylene units, and they have been used both internally and externally in products that are designed for animal and human uses. The physicochemical characterizations of Carbopol-Poloxamer gels were conducted as a first step for buccal administration with bioadhesiveness and gelling property.

The influence of neutralization of Carbopol on the viscosity and bioadhesiveness was studied on the various Carbopol gels. The bioadhesive capacity of gels obtained from Carbopol 934 and Poloxamer 407 was determined using a tensile tester. To investigate the interaction between triamcinolone acetonide and two polymers, Fourier transform infrared (FTIR) spectrometry and X-ray diffraction (XRD) studies were carried out with Carbopol-Poloxamer solid dispersions.

MATERIALS AND METHODS

Materials

The Carbopol 934 was obtained from B.F. Goodrich (Cleveland, OH), and the Poloxamer 407 was from BASF (Ludwigshafen, Germany). The triamcinolone acetonide was a gift from Shinpoong Pharmaceutical Company (Korea). Tris(2-amino-2(hydroxymethyl)-1,3 propanediol) and all other reagents were analytical grade and were used without further purification.

Preparation of Carbopol-Poloxamer Gels

Aqueous-based Carbopol 934 gels were prepared with the various concentrations of Carbopol. After continuous stirring at 1200 rpm for 5 min, the gel samples were left to hydrate completely and then centrifuged at 3000 rpm for 30 min to remove air bubbles. Each gel was adjusted to pH 4, 5, 6, 7, and 8 with various neutralizing agents such as Tris, triethanolamine, and NaOH solution.

Mucoadhesive gel containing 1% triamcinolone acetonide gels was prepared with 2% Carbopol and 20% Poloxamer gels prepared by the cold method (5). Cold Poloxamer solution containing drug was added to Carbopol solution under magnetic stirring and left at 5°C overnight in a refrigerator to complete polymer desolvation.

Measurement of Viscosity of Carbopol Gels

The viscosity of each gel was measured with a viscotester (VT500/501, Haake, Germany). The sensor system was NV, MV, SV, which is primarily used for viscosity measurements of high-viscosity liquids and pastes such as greases, creams, ointments, plastisols, and the like working in the low to medium shear rate range.

Measurement of the Bioadhesive Strength

Adhesive capacity was determined by measuring the maximum detachment force and the adhesion work using a tensile tester, Instron (Autograph, Shimadzu, Japan). The force of adhesion, or peak adhesion strength, refers to the peak height of the stress-strain curve, which measures the force required to separate the prove from the substrate. Cyanoacrylate adhesive was used to fix the porcine buccal mucosa to the upper and lower support. The Carbopol-Poloxamer gel was placed on the both supports. On contact of the gel-mucosa, a force was applied during a period of time. This procedure was carried out at a defined rate until the complete detachment of the components was achieved. The adhesion work was calculated as gram force (gf).

Spectroscopic Characterization

The 1:4 weight ratio coprecipitates and physical mixtures of triamcinolone acetonide and Carbopol or Poloxamer were prepared. The coprecipitates were prepared by an evaporating method after dissolving triamcinolone acetonide and Carbopol or Poloxamer in methanol. Residual organic solvent was removed by a speed-vacuum apparatus. The physical mixtures of triamcinolone acetonide and Carbopol or Poloxamer were prepared by simple blending.

The IR spectra for the test samples were obtained by the KBr disk method using an FTIR spectrophotometer

(FTIR-300E, Jasco, Japan). Powder XRD patterns were measured using a Rigaku X-ray diffractometer (D/max-1200, Tokyo, Japan). The target was copper tube (nickel filter), 30 kV, 5 mA.

RESULTS AND DISCUSSION

Viscosity

The viscosity of 0.5% Carbopol gels of various pH was determined at various shear rates (Fig. 1). As the shear rate increased, the viscosity of Carbopol gel decreased. The influences of changing the neutralizing agents, such as Tris, triethanolamine, and NaOH solution, for adjusting the pH of Carbopol gels were less marked (data not shown). In particular, samples neutralized with Tris consistently showed less high viscosity than samples neutralized with other agents. This effect might be associated with charges being more closely bound into the polymer network in the Tris-neutralized gels. The choice of neutralizing agent did not affect the viscosity of Carbopol.

Figure 2 shows the viscosity of Carbopol gel of various concentrations and various pH. The increase in Carbopol concentration to about 3% caused the increased viscosity and thereafter showed slightly increased viscosity. Marked differences were noted in viscosity of Carbopol gels of various pH. The increase of pH in various concentrations of Carbopol gels showed increased viscosity, showing the highest viscosity when neutralized to pH 6 (Figs. 1 and 2). This is related to the increase in ionization as a result of increased pH, which leads to an increase in electrostatic repulsion between adjacent carboxylic groups and the subsequent expander polymer network (6).

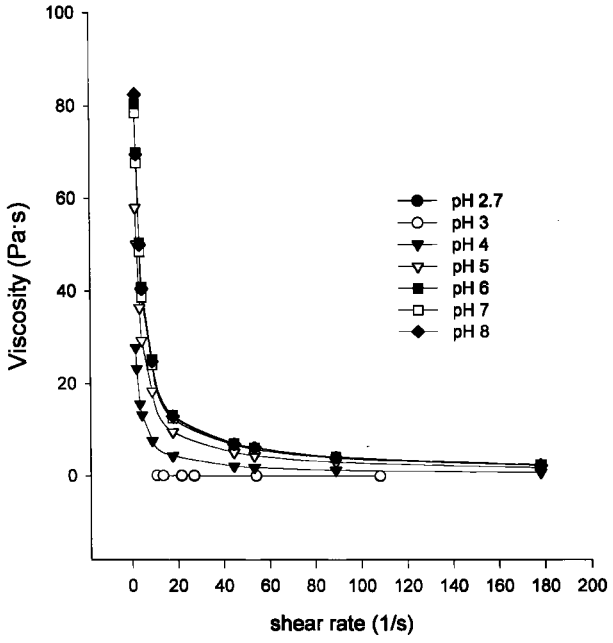

Figure 1. Viscosity of 0.5% Carbopol gels of various pH.

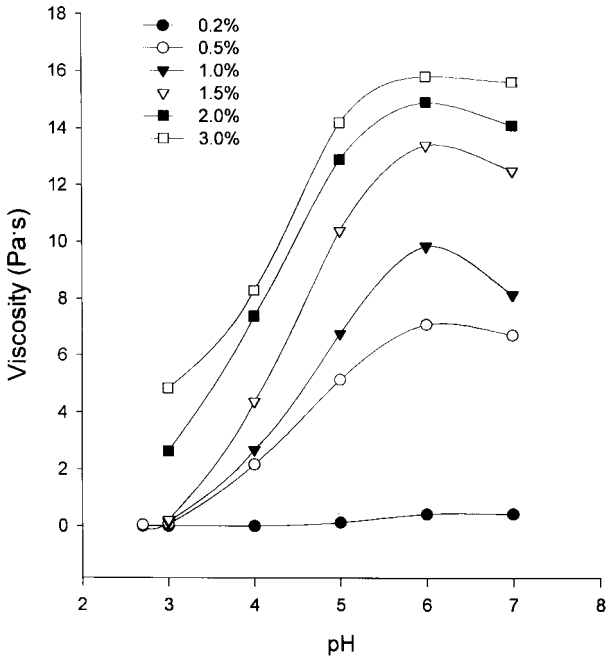

Figure 2. Viscosity of various Carbopol gels at various pH at a shear rate of 44.5.

Unneutralized Carbopol gels show significantly weaker gel structure, as expected, due to the constricted gel network. The structures of these unneutralized systems are predominantly built up by hydrogen bonds, which are easily breakable under shear stress (Fig. 1). When Carbopol is exposed to water, the polymer begins to uncoil, generating an increase in viscosity and gel formation (7). In an alkaline environment, the carboxyl groups ionize, generating negative charges along the polymer backbone. Electrostatic repulsion of the negative charges causes uncoiling and expansion of the molecule, which results in polymer swelling and elastic gel formation.

Bioadhesion with Various Mucosa

The bioadhesive material must come into close contact with the tissue for bioadhesion to occur. Carbopol resins,

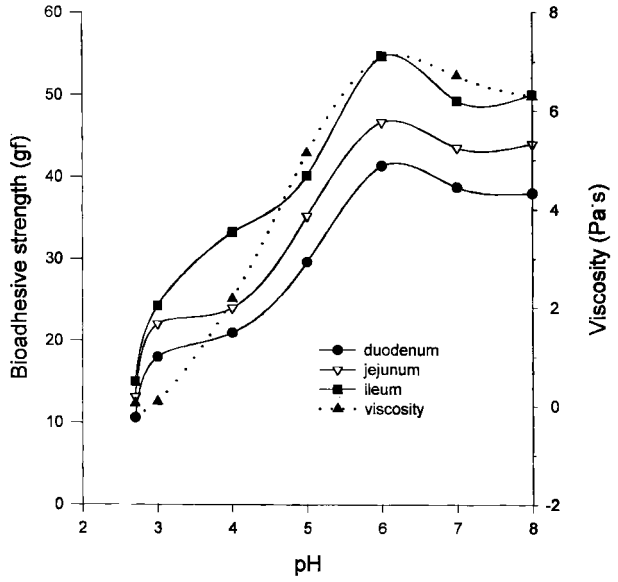

Figure 3. The bioadhesive strength between the mucosa and 0.5% Carbopol gels of various pH.

due to their chemical nature, are high molecular weight polymers that readily swell in water, providing a large adhesive surface for maximum contact with the mucin (the glycoprotein predominant in the mucous layer) and may provide excellent bioadhesiveness for many reasons.

These studies of the viscosity and bioadhesive properties of the 0.5% Carbopol gels adjusted to various pH, both in unneutralized and pH-adjusted states, were carried out using a detachment force test (Fig. 3). The tensile tester is widely used to evaluate the adhesive capacity of different polymers and formulations (8–11). This method determines the maximum work or force needed to separate two materials that exist in intimate contact.

A relationship between the viscosity and bioadhesive strength was shown from the neutralized Carbopol gels. As the viscosity of Carbopol gel increased by adjusting the pH, the bioadhesive strength increased. The rheological properties of bioadhesive gels have been investigated by several authors, although there is still debate regarding the relationship between these properties and bioadhesive performances. According to Tur (6), polymers showed strongest adhesion in the saline medium, intermediate in the acidic gastric fluid, and weakest in the buffered intestinal fluid. In gastric fluid, the mucin carboxylic acid group in the polymer structure will be in protonated form with a small degree of ionization, resulting in a limited amount of uncoiling of the polymer; intermediate adhesion may occur through hydrogen bonding of the unionized carboxylic groups.

At low pH (5.0 or less), less than 10% of the Carbopol acid group will be ionized, resulting in relatively little stiffening by electrostatic charge repulsion and relatively little swelling compared to fully neutralized Carbopol systems. In this regime, hydrogen bonding to polysaccharides or directly to proteins is probably the major mechanism for bioadhesion. The pK_a of Carbopol polymers is 6.0 ± 0.5. Above that point, the carboxylic acid groups are ionized greatly, thus reducing hydrogen bonding. Under more alkaline conditions, the Carbopol gels are very highly swollen, and the chains are stiffened by electrostatic repulsion of the anionic charges along backbone.

The increase of Carbopol concentration in the gels showed the increased bioadhesive strength. The intestines at various sites represent better bioadhesive strength compared to the buccal mucosa. The lower part of the intestine represented greater bioadhesion. Above 2% concentration, the bioadhesive property did not increase further (Fig. 4). Tamburic and Craig (12) reported that, once neutralized, Carbopol 934P gels do not show marked differences in bioadhesive properties. In general, the effects of changing the neutralizing agent on the bioadhesive performance are small compared to the effects

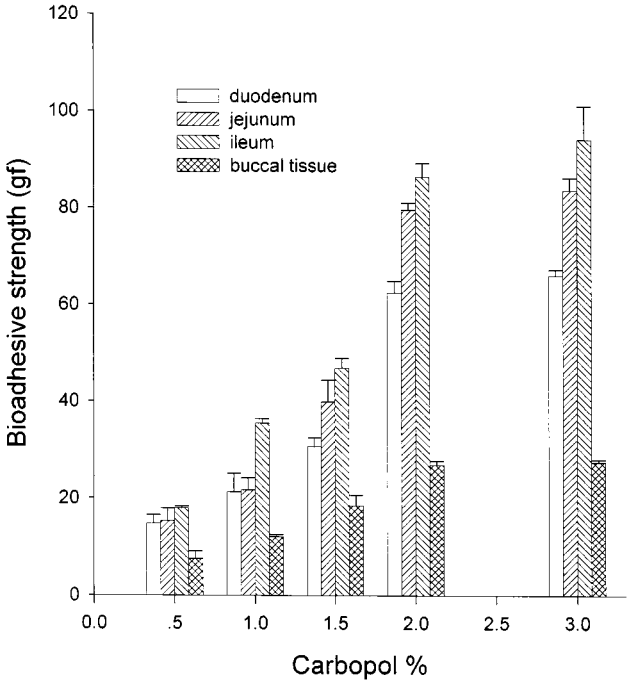

Figure 4. The bioadhesive strength between the mucosa and Carbopol–20% Poloxamer gels.

of changing the polymer. Information regarding the material properties of the gels is of use when considering the choice of polymer for any particular application, but is also of interest in a relationship between the flow properties of gels and their bioadhesive performance (13).

The study suggests that the relationship between the viscosity of Carbopol gel systems and bioadhesion may facilitate optimization of mucoadhesive performance, leading to the development of more effective bioadhesive dosage forms. To prepare the bioadhesive systems, one must control the degree of ionization of the polymer by manipulating the pH of the media or, alternatively, choose a bioadhesive with a pK_a that can provide a suitable extent of ionization. This phenomenon is essential in the design of bioadhesive dosage forms since external pressure cannot be applied to them in the mucosal membranes (6).

Infrared Spectroscopy

The solubility of triamcinolone acetonide in Poloxamer solution is highly increased due to solubilizing action, and there might be a possibility that different phases are present. To elucidate the additional physicochemical properties of the drug molecule in the gel state, IR spectroscopy was carried out for the test preparations. The IR spectra of the 1:4 ratio triamcinolone acetonide–Poloxamer physical mixture and the same ratio solid dispersion are shown in Fig. 5 and those with Carbopol in Fig. 6. The 3400-cm^{-1} band of —OH stretching vibration clearly visible in the spectrum of triamcinolone acetonide is also discernible in the spectra for physical mixture and solid dispersion. The IR spectra of the solid dispersion showed the same absorption bands as the physical mixtures, illustrating the mere presence of triamcinolone acetonide, Carbopol, and Poloxamer (Figs. 5 and 6). It presumably suggests that the drug molecule is present in an unchanged state in the solid dispersion.

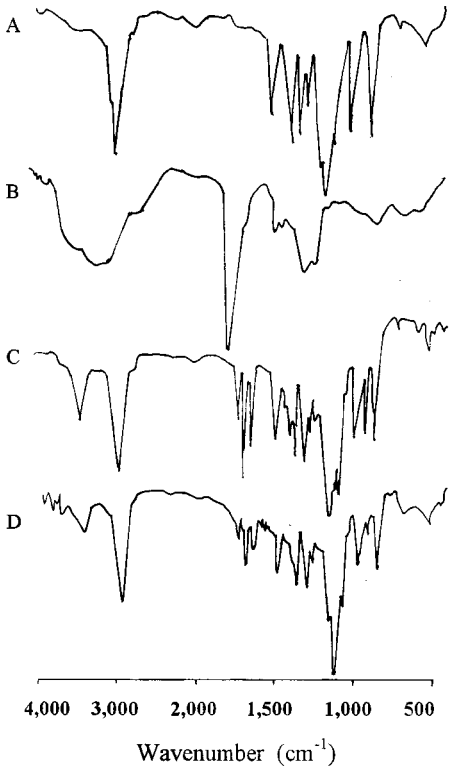

Figure 5. IR spectra of Poloxamer test materials: (A) triamcinolone acetonide (TA); (B) Poloxamer 407; (C) 1:4 ratio TA–Poloxamer 407 physical mixture; (D) 1:4 ratio TA–Poloxamer 407 solid dispersion.

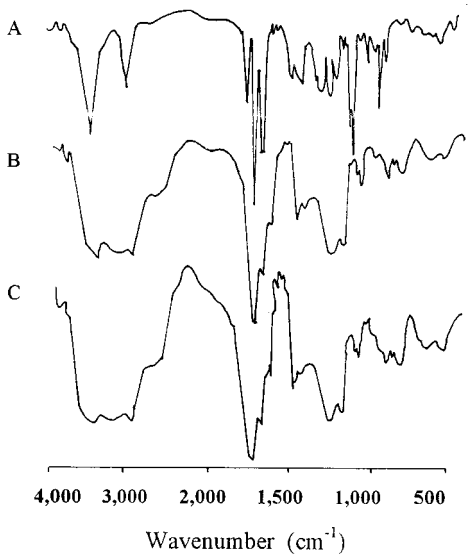

Figure 6. IR spectra of Carbopol test materials: (A) Carbopol 934; (B) 1:4 ratio TA–Carbopol 934 physical mixture; (C) 1:4 ratio TA–Carbopol 934 solid dispersion.

X-Ray Diffraction

X-ray diffraction studies were carried out to unravel the additional crystalline modification. Figure 7 shows the X-ray diffractograms for the 1:4 ratio triamcinolone acetonide–Poloxamer physical mixture and the same ratio solid dispersion. The physical mixture and solid dispersion showed crystallinity supposedly due to the presence of the crystalline form. It presumably suggests that

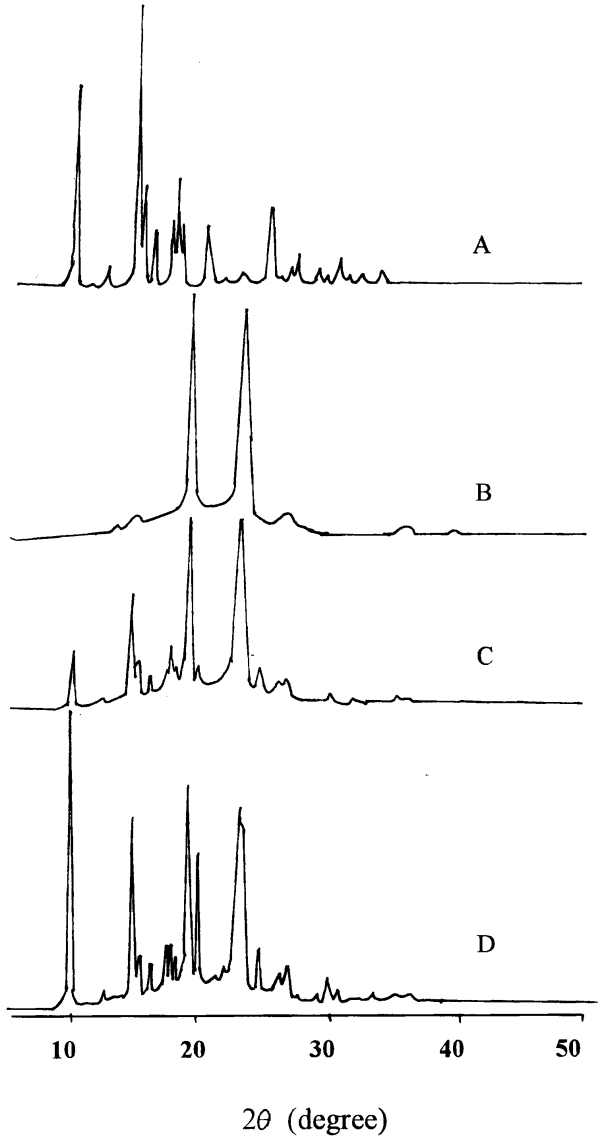

Figure 7. X-ray diffractograms of test materials: (A) triamcinolone acetonide (TA); (B) Poloxamer 407; (C) 1:4 ratio TA–Poloxamer 407 physical mixture; (D) 1:4 ratio TA–Poloxamer 407 solid dispersion.

the drug molecule is present in a crystalline state in the solid dispersion.

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