Factors Affecting the Bioadhesive Property of Tablets Consisting of Hydroxypropyl Cellulose and Carboxyvinyl Polymer[1)]

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The bioadhesive property of tablets consisting of hydroxypropyl cellulose (HPC) and carboxyvinyl polymer (CP) was investigated using the mouse peritoneal membrane. The adhesion force was significantly affected by the mixing ratio of HPC and CP in the tablet, and the weakest adhesion force was observed at the ratio of 3:2 (HPC:CP). Interpolymer complex formation was confirmed between HPC and CP in the acidic medium by turbidity and viscosity measurements. The interaction between CP carboxyl groups and HPC molecules was considered to be a possible mechanism for this complex formation on the basis of a Fourier-transform infrared spectroscopy. These observations suggested that the adhesion force of the HPC–CP tablet to the mucous membrane was significantly affected by the interpolymer complex formation between HPC and CP.

Keywords mucous adhesion; peritoneal membrane; compressed tablet; hydroxypropyl cellulose; carboxyvinyl polymer; interpolymer complex; turbidity; viscosity; infrared spectroscopy

Introduction

Mucosal adhesive dosage forms have been developed as a new type of external preparation that may make treatment more effective and safe, not only for topical diseases, but also for systemic ones.[2,3)] A typical preparation is an oral mucosal adhesive tablet developed for the treatment of aphtha, which is now commercially available under the brand name of Aftach.[4,5)] Hydroxypropyl cellulose (HPC) and carboxyvinyl polymer (CP) have been used as principal excipients of this tablet in order to obtain the appropriate adhesion property to the oral mucous membrane and to control the drug release from the tablet.[4,5)] The purpose of the present study is to elucidate factors affecting the bioadhesion property of compressed tablets consisting of HPC and CP. In this connection, the interpolymer complex formation between HPC and CP seems to be particularly noteworthy. The existence of the interaction was confirmed by turbidity and viscosity measurements. Furthermore, Fourier-transform infrared spectroscopy (FT-IR) was employed to analyze the interaction mechanism. The adhesion force of HPC–CP tablets to the mucous membrane was evaluated by utilizing the mouse peritoneal membrane.[6)] The use of a glass plate as a model of the mucous membrane was also investigated in order to examine the effect of moisture on the adhesion force of HPC–CP tablets.

Experimental

Materials HPC marketed as Hydroxypropyl cellulose-M was purchased from Nippon Soda Co., Ltd. The viscosity of a 2% HPC aqueous solution was 240 cP at 20 °C as determined with a Tokyo Keiki BL type viscometer. CP marketed as "Carbopol 934" was purchased from B. F. Goodrich Co. The viscosity of a 0.2% CP aqueous solution (at pH 7.0) was 4510 cP at 20 °C as determined with the same apparatus described above. For the FT-IR study, CP was used after being washed with chloroform and dried in a vacuum at room temperature for 3 d. For the other studies, HPC and CP were used without further treatment.

Turbidity Measurement HPC solution (2.5 ml; 0—0.02%) was mixed with CP solution (2.5 ml; 0—0.02%) at 37 °C for 1 h to prepare the sample solution. Buffer solutions (pH 3.0, 4.5 and 6.0), prepared from 0.05 N HCl, 0.05 M CH_3COONa, 0.05 M KH_2PO_4, and/or 0.05 M Na_2HPO_4, were used to dissolve samples. Total polymer concentration was fixed at 0.01% in all samples. The turbidity of each sample solution was determined at 600 nm, where there was no absorption due to the polymers in solution, using a Hitachi 200-20 spectrophotometer.

Viscosity Measurement HPC solution (10 ml; 0—1.0%) was mixed with CP solution (10 ml; 0—1.0%). The sample solution was then incubated at 30 °C for 7 d. Total polymer concentration was fixed at 0.5% in all samples. After centrifugation for 20 min at 15000 rpm in a Hitachi SCR 20B centrifuge, the viscosity of the supernatant solution was determined at 37 °C by the use of an Ubbelohde viscometer. Buffer solution (pH 3.0), which consisted of 0.05 N HCl and 0.05 M CH_3COONa, was used to prepare the sample solutions.

Preparation of the Solid Complex HPC solution (20 ml; 0—0.1%) was mixed with CP solution (20 ml; 0—0.1%). The sample solution was then incubated at 37 °C for 10 d. Total polymer concentration was fixed at 0.05% in all samples. After the removal of water in the sample solution by the use of a rotary evaporator, the solid complex that remained was dried in a vacuum for 3 d at room temperature.

IR Absorption Spectroscopy FT-IR spectra of HPC-CP solid complexes were measured using a Jasco model FT/IR-5 spectrophotometer (KBr disk method).

Adhesion Force Measurement Tablets with a diameter of 5 mm were prepared by compressing 90 mg of a mixture of HPC and CP in a mixing ratio of 4:1, 3:2, 1:1, 2:3, or 1:4, at a pressure of 20 kg/cm^2, using a Shimadzu hydraulic press. HPC and CP powders retained in a 200 mesh sieve (75 μm) and passing through a 60 mesh (250 μm) were used to prepare the tablets. After a tablet had been put on the mouse peritoneal membrane, a constant weight (20 g) was applied on the table for 1 min to complete the adhesion. The adhesion force (g/mm^2) was then measured by means of the stickiness test apparatus previously reported.[6)] Male ddY strain mice weighing 18 to 22 g were used as experimental animals. The mice were killed by cervical dislocation, and the peritoneal membrane was extracted and immersed in a saline solution at 37 °C. The membrane was used within 5 min after extraction. Before the measurement, the surface of the peritoneal membrane was washed with purified water and the residual water on the surface was removed with a filter paper. In the case of the adhesion test to a glass plate, the tablet surface was immersed in water for 3—30 s, and the adhesion force was determined in the same way as described above after the removal of residual water on the surface with a filter paper.

Results and Discussion

Confirmation of Interpolymer Complex Formation Figure 1 shows the turbidity as a function of weight ratio of HPC–CP in media of various pH values. Maximum turbidity was found at the weight ratio of 3:2 in the acidic medium (pH 3.0). This result suggested that the solid complex of HPC and CP might be formed in the acidic medium at the weight ratio of 3:2. No solid complex formation was observed in the higher pH region (pH 4.5 and 6.0). Since the pK_a value of acrylic acid, the main unit monomer of CP, was reported to be 4.25 at 25 °C,[7)] the dissociation of carboxyl groups of CP might be important

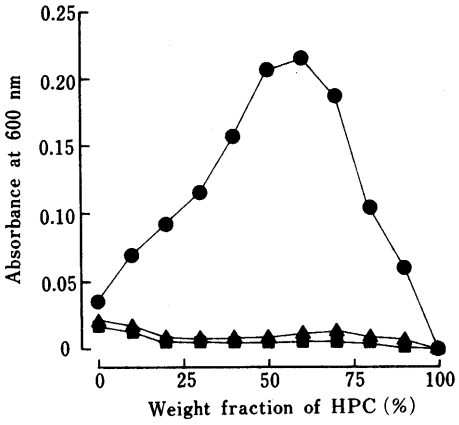

Fig. 1. Turbidity of the HPC–CP System as a Function of Polymer Mixing Ratio in Media of Various pH Values at 37 °C (Total Polymer Concentration = 0.01%)

Each point represents the mean of three determinations. pH values: ●, 3.0; ▲, 4.5; ■, 6.0.

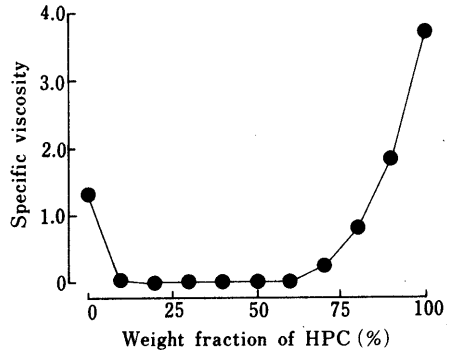

Fig. 2. Viscosity of Supernatant Solution in the HPC–CP System as a Function of Polymer Mixing Ratio at pH 3.0 and 37 °C (Total Polymer Concentration = 0.5%)

Each point represents the mean of three determinations.

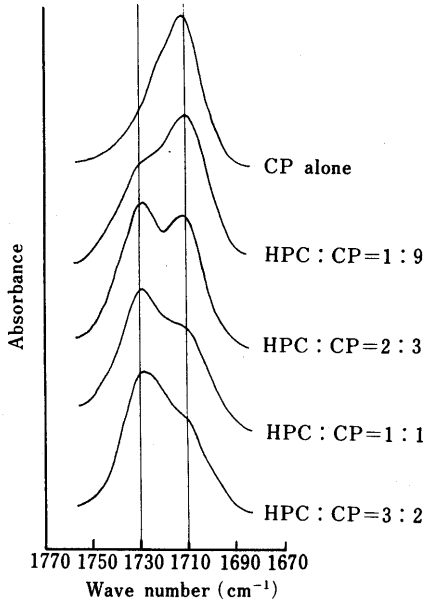

Fig. 3. FT-IR Spectra of HPC–CP Complexes

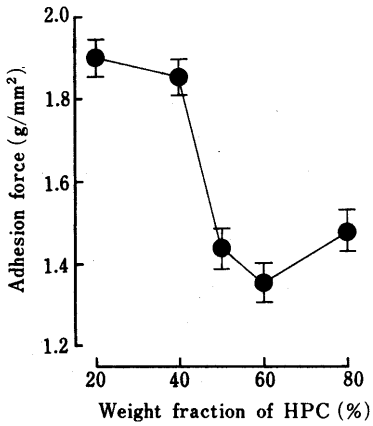

Fig. 4. Adhesion Force of HPC–CP Tablet to the Mucous Membrane as a Function of Polymer Mixing Ratio

Each point represents the mean ± S.E. of five determinations.

for the balance of complexation and decomplexation. Figure 2 shows the viscosity of the supernatant of HPC–CP mixture solution as a function of weight ratio of HPC and CP mixture solution as a function of weight ratio of HPC and CP in the acidic medium (pH 3.0). When the weight fraction of HPC in samples was from 10 to 60%, the viscosity of the supernatant in the HPC–CP solution was observed to be almost the same as that of the medium. In the case of HPC alone or CP, the viscosity of these solutions increased continuously with increase of polymer concentration. Therefore, the decrease of viscosity observed in the HPC–CP mixture system showed that the solid complex was formed in the acidic medium and was removed by the centrifugation.

Next, the FT-IR spectra of HPC–CP solid complexes were determined. Figure 3 shows FT-IR spectra of HPC–CP complexes at various mixing ratios in the region of carbonyl absorption. In the case of CP alone, a single peak at 1710 cm^{-1} was observed and it was assigned to the dimer carboxyl structure of CP.[8] When a small amount of HPC was contained in the sample (HPC : CP = 1 : 9), a new peak appeared at 1730 cm^{-1}. The increase of HPC content in the complex led to enhancement of the peak at 1730 cm^{-1} and a decline of the peak at 1710 cm^{-1}. Since no peaks of the HPC molecules were observed in this region (1700—1740 cm^{-1}), the peak observed at 1730 cm^{-1} was assigned to the CP carboxyl groups bound with HPC.[8] As shown in Figs. 1 and 2, the stoichiometric ratio of the solid complex precipitated in the acidic medium was supposed to be 3 : 2 (HPC : CP, w/w). The peak at 1710 cm^{-1} almost disappeared at the ratio of 3 : 2 (HPC : CP), suggesting that a stable solid complex was formed at this weight ratio. Although no conspicuous change in the IR spectrum of HPC due to the complex formation was observed, the peak shift of CP carboxyl groups, which was brought about by the increase of HPC content, might suggest possible hydrogen bonding between CP carboxyl groups and HPC molecules. It is known that the carboxyl groups in polyacrylic acid, which is a similar compound to CP, interact with other polymers such as polyoxyethylene and polyvinylpyrrolidone through hydrogen bonding as a primary binding force.[9] These complexes are dissociated by ionization polyacrylic acid.[9] These facts also support the hydrogen bonding between HPC and CP since a solid complex was

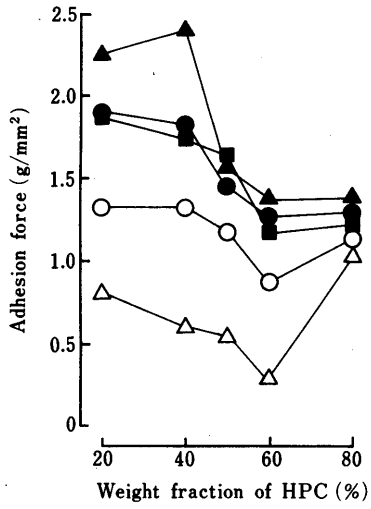

Fig. 5. Adhesion Force of HPC–CP Tablets to a Glass Plate as a Function of Polymer Mixing Ratio

Each point represents the mean of three determinations. Immersion time of tablet in water: ●, 3 s; ▲, 5 s; ■, 10 s; ○, 20 s; △, 30 s.

obtained in the acidic medium, but not at higher pH (4.5 and 6.0), as shown in Fig. 1.

Adhesion Property of HPC–CP Tablet Figure 4 shows the adhesion force of HPC–CP tablet to the mucous membrane at various mixing ratios of HPC and CP. The weakest adhesion force was observed at the mixing ratio of 3:2. In a previous study,[6] however, no clear relationship was found between the mixing ratio and the adhesion force. Although the reason for this is not clear, the method used to obtain adhesion of the tablet to the mucous membrane before the measurement might be very important. In the previous paper,[6] the tablet was put on the membrane for 10 min to complete the adhesion. However, too long an adhesion time to the membrane will allow the progress of gel layer formation at the boundary between the tablet and membrane, and this may have caused the discrepancy. In this study, we put the tablet on the membrane for exactly 1 min, applying a constant pressure as described in Experimental. Furthermore, the adhesion data were obtained with only fresh peritoneal membranes. Thus, we were able to observe that the bioadhesion property of HPC–CP tablets is strongly dependent upon the interpolymer complex formation (Figs. 1—4).

It was also observed in the previous study[6] that the adhesion force was closely related to the moisture content on the mucous membrane. Namely, the tablet did not stick to a very moist membrane, but stuck tightly to one with little moisture. In the measurement of adhesion force to the mucous membrane, it is difficult to control the amount of moisture on the surface of the mucous membrane. We then tried to find a suitable model of the mucous membrane in a preliminary study with various candidate materials. A glass plate was found to be most suitable as a model of the mucous membrane. Figure 5 shows the adhesion force of HPC–CP tablets to a glass plate at various mixing ratios of HPC and CP. Before the measurement of adhesion force, each sample tablet was immersed in water for an appropriate time in order to supply moisture at the boundary between the tablet and the glass plate. In comparison with the result observed in Fig. 4, a proper adhesion force was obtained when the tablet was immersed in water for a relatively short period (3—5 s). The adhesion force at these immersion times correlated well with that measured in the mucous membrane ($r=0.931$ and 0.951). Figure 5 also shows that the interpolymer complex formation between HPC and CP inhibits the adhesion force of the tablet, as observed in the mucous membrane. The adhesion force gradually decreased with increase of the immersion time in water, and no adhesion was obtained without moisture at the boundary between the tablet and the glass plate. Therefore, very thin and strong gel layer formation at the boundary might be necessary for the adhesion. In this connection, the interpolymer complex formed in the gel layer might act as an inhibitor of the adhesion due to its hydrophobicity.

Although further studies taking account of the molecular structures of HPC and CP should be made to elucidate precisely the mechanism of the bioadhesion, we can conclude that the interpolymer complex formation between HPC and CP significantly affects the adhesion property of the tablets to the mucous membrane. Experimental results obtained in this study should be helpful for the further development of mucosal adhesive dosage forms.

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