Design of Mucoadhesive Polymeric Films Based on Blends of Poly(acrylic acid) and (Hydroxypropyl)cellulose

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Mixing of aqueous solutions of poly(acrylic acid) and (hydroxypropyl)cellulose results in formation of hydrogen-bonded interpolymer complexes, which precipitate and do not allow preparation of homogeneous polymeric films by casting. In the present work the effect of pH on the complexation between poly(acrylic acid) and (hydroxypropyl)-cellulose in solutions and miscibility of these polymers in solid state has been studied. The pH-induced complexation−miscibility−immiscibility transitions in the polymer mixtures have been observed. The optimal conditions for preparation of homogeneous polymeric films based on blends of these polymers have been found, and the possibility of radiation cross-linking of these materials has been demonstrated. Although the γ-radiation treatment of solid polymeric blends was found to be inefficient, successful cross-linking was achieved by addition of *N*,*N*′-methylenebis(acrylamide). The mucoadhesive potential of both soluble and cross-linked films toward porcine buccal mucosa is evaluated. Soluble films adhered to mucosal tissues undergo dissolution within 30−110 min depending on the polymer ratio in the blend. Cross-linked films are retained on the mucosal surface for 10−40 min and then detach.

Introduction

During the last two decades, the development of novel mucoadhesive dosage forms has received considerable interest. The progress in this field has recently been summarized in a number of reviews.[1−5] Mucoadhesive drug delivery systems can be administered via various routes such as ocular, nasal, gastrointestinal, vaginal, and rectal, which makes them extremely attractive for the development of new dosage forms.

Mucoadhesion is a complex phenomenon and its mechanisms are not well understood. The theories that are most commonly used to explain mucoadhesion are the electronic, absorption, diffusion, and wetting theories.[6] The electronic theory assumes that transfer of electrons occurs between the mucus and mucoadhesive due to differences in their electronic structures. This electron transfer leads to the formation of a double electric layer at the interface and results in attraction between the dosage form and the substrate. The absorption theory concerns the attraction between the mucus and the mucoadhesive achieved via molecular bonding caused by secondary forces such as hydrogen bonding and van der Waals forces. The diffusion theory considers interpenetration and physical entanglement of the mucus protein and polymer chains of the mucoadhesive. The wetting theory correlates the surface tension of the mucus and the mucoadhesive with the ability of the mucoadhesive to swell and spread on the mucus layer. However, none of these theories alone can explain mucoadhesion for varied mucoadhesive formulations.

Some of the polymeric structural characteristics necessary for mucoadhesion can be summarized as follows: (1) strong hydrogen bonding groups, for example, carboxyl, hydroxyl, amino, and sulfate groups; (2) strong anionic or cationic charges; (3) high molecular weight; (4) chain flexibility; and (5) surface energy properties favoring spreading onto mucus.[1] Poly(acrylic acid) (PAA) and its derivatives have been shown to have good mucoadhesive properties, but their tendency to cause irritation has limited their broad application as mucoadhesives.[7] One of the ways to overcome this obstacle is mixing PAA with nonionic polysaccharides, which show excellent biocompatibility. A number of researchers have developed mucoadhesive formulations based on mixtures of PAA with water-soluble cellulose ethers such as (hydroxypropyl)cellulose (HPC) and (hydroxypropyl)methylcellulose (HPMC).[8−13] Although it was shown that these formulations have excellent performance as dosage forms, several limitations of using these polymeric mixtures can be pointed out. In fact these limitations arise from a strong hydrogen bonding between carboxylic groups of PAA (or its derivatives) and proton-accepting groups of cellulose ether, resulting in formation of interpolymer complexes (IPC). The complexation between PAA and HPC (or HPMC) is accompanied by phase separation and precipitation of IPC, which makes the preparation of homogeneous polymeric films based on this blend difficult. For this reason, most PAA−HPC and PAA−HPMC dosage forms were prepared as tablets.[8−13] These precipitates also have a certain stoichiometry, which limits preparation of materials with a broad range of PAA−HPC ratios. It was also demonstrated that the complexation of PAA with cellulose ethers reduces the mucoadhesive ability of the formulation compared to pure PAA.

Previously[14] we have reported a preparation of polymeric films based on PAA−HPC using completely neutralized PAA to prevent the complex formation. Although this attempt resulted in formation of polymeric films, the physicochemical and mechanical properties of these materials were rather poor

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because of complete immiscibility between poly(sodium acrylate) and HPC.

In the present work we have studied the complexation in solutions of PAA and HPC, established the optimal conditions for preparation of PAA−HPC polymeric films, developed a technology for cross-linking of these materials with γ-radiation, and assessed their mucoadhesive ability toward porcine buccal mucosa.

Experimental Section

Materials. Poly(acrylic acid) (PAA) with weight-average molecular weights (M_w) of 2000, 100 000, 230 000, and 450 000 and (hydroxypropyl)cellulose (HPC) with M_w 100 000 and degree of substitution 66−70% (catalog no. 191884, lot 09604HU-032) were purchased from Aldrich and used without further purification. Pyrene as a luminescence probe and *N*,*N*′-methylenebis(acrylamide) (BAA) as a cross-linking agent were purchased from Sigma and used without further purification.

Determination of IPC Composition. The composition of IPC in aqueous solutions was estimated by titration procedure as described below. A certain amount of PAA and HPC were dissolved in distilled water in a conical flask to obtain 0.01 unit·mol/L aqueous solutions of polymers. Then 10 mL of PAA and HPC were transferred into vials and 0.5 mol/L HCl was added to each polymer solution to adjust the pH. The pH of solutions was controlled with a digital pH meter with a precision of ±0.01 pH unit (Ion Meter 3345, Jenway Ltd.). Then a titrant solution (HPC) was added to PAA solution stepwise in volume increments of 1 mL under stirring to establish equilibrium.

Turbidimetric Measurements. The changes in turbidity of aqueous mixtures of PAA and HPC were examined at 400 nm with a UV−vis 2401 PC spectrophotometer (Japan, Shimadzu) and reported as optical density (D), which is linearly proportional to the true turbidity for transmittance <90%.

Viscometric Measurements. The capillary Ubbelohde viscometer was used to measure the viscosity of PAA−HPC polymer solutions. Prior to each measurement, the viscometer was thoroughly cleaned and rinsed with the distilled water and acetone to remove contaminants. Finally, it was dried in an oven at 50 °C. The viscosity measurements were performed at 25.0 °C. The solution temperature was controlled by a thermostat in a circulating bath and monitored by a thermometer with a resolution of 0.1 °C. The flow time of distilled water through the viscometer was 120 s.

Luminescence Spectroscopy. Microscopic polarity of IPC solutions was tested by a Perkin-Elmer LS 55 luminescence spectrometer (Perkin-Elmer Instruments), with a pyrene probe. In these experiments the concentration of pyrene was 2×10^{-6} mol/L, scanning speed = 100 nm/min, excitation wavelength λ_{ex} = 335 nm. The polarity was determined through the intensity ratio (I_3/I_1) of the third (383 nm) to the first vibronic peak (373 nm) of emission fluorescence spectrum of pyrene in the presence of polymers.

Preparation of Polymeric Films. Films of PAA and HPC were prepared by mixing 0.1 unit·mol/L polymer aqueous solutions with different ratios. The solutions were stirred at a constant rate and at ambient temperature for 20 min after addition of small amounts of 0.5 mol/L HCl or NaOH to adjust the pH. This viscous solution was poured onto polyethylene plates with subsequent solvent evaporation for several days at room temperature to form a film. Finally, the film samples were dried at 35 °C in a vacuum oven for 24 h to remove any traces of water.

Film Transparency Measurements. To measure the transparency of the films, specimens of 10 mm width were put into a quartz cell and then scanned with a Shimadzu UV−Vis 2401 PC spectrophotometer (Japan) at the wavelength 400 nm.

Scanning Electron Microscopy. Morphological analysis of the cross-sections of the films was carried out with a Superprobe 733 electron probe microanalyzer (JEOL, Japan) at an accelerating potential of 20 kV with the help of an Inka energy-scanning spectrometer (Oxford Instruments). A magnification of ×1500 was used for PAA−HPC films prepared at different pH and pure PAA, and ×3000 was used for pure HPC. Before the SEM observations, gold was sputtered for 30 min on the cross-sections of the films in a vacuum by use of a fine coat instrument (JEOL, Japan).

Radiation Cross-Linking of PAA−HPC Films. Irradiation of PAA, HPC, and PAA−HPC film samples (30 × 30 mm) with or without cross-linking agent BAA was carried out in plastic bags at the cobalt-60 cell facility MRX-γ-25 of the Institute of Nuclear Physics, Almaty, Kazakhstan at various doses, ranging from 0 to 302 kGy, at a dose rate of 1.4 kGy/h. To remove the soluble part, the cross-linked PAA−HPC films were washed in 1 mol/L NaOH solution at 35 °C for 3 h and rinsed by running distilled water for 1 h.

Gel Fraction Measurements. The gel fractions were calculated as the ratio of the weight of the dried gel to the initial weight of the polymer:

$$\mathrm{GY} = m/m_0$$

where m is the weight of the dry gel and m_0 is the weight of the original sample.

Swelling Behavior of PAA−HPC Radiation Cross-Linked Films. Swelling kinetics of radiation-modified PAA−HPC films was measured by the gravimetric method. Dry samples preliminarily weighed in the form of disks with a diameter of 13 mm and weight ≈0.01 g were immersed into a buffer solution with a certain pH value. The samples were removed from the buffer at set time intervals, the residual moisture on the film surface was removed by means of a filtering paper, and the samples were weighed. The swelling degree of the films was calculated by the following formula:

$$\alpha = (m - m_0)/m_0$$

where m −is the weight of a swollen film at different time intervals and m_0 −is the weight of a dry film. A swelling degree was defined in several parallel experiments, and average values were calculated.

Assessment of Bioadhesive Properties of PAA−HPC Films. Porcine buccal mucosa tissue was obtained from a local slaughterhouse. After removal of connective tissues, the buccal mucosa was treated with distilled water and stored in a refrigerator at −17 °C. For mucoadhesive tests, the disk-shaped tissue with diameter of 20 mm was glued onto a precleaned polyethylene slide with cyanoacrylate adhesive. The tissue slide was then secured onto a holder with a sleeve fastener of mechanical mixer Eurostar Power 1 Kika Labortechnik (Germany). Polymer disks of PAA−HPC films with a diameter of 15 mm were hydrated by placing 20 μL of distilled water onto their surface, then brought into contact with mucosal tissue and immersed into buffer solution (pH 6.86) and maintained at 37 ± 1 °C under stirring at 30 rpm.

Results and Discussion

Complexation between PAA and HPC in Aqueous Solutions. Various physicochemical techniques can be applied for investigation of interpolymer complexation in solutions. The most common are viscometric and turbidimetric techniques. The viscometric technique allows monitoring of the conformational changes occurring with macromolecules upon complexation, and the turbidimetric technique measures the aggregation of hydrophobic IPC particles. These two techniques were applied in the present work to get primary information about complex formation between PAA and HPC. Figure 1 shows the results of viscometric and turbidimetric titration of an aqueous solution of PAA by a solution of HPC performed at different pH values. A strong effect of pH can be observed from the data obtained. The experiments performed at pH 4.2 result in featureless titration curves showing neither turbidity appearance nor the

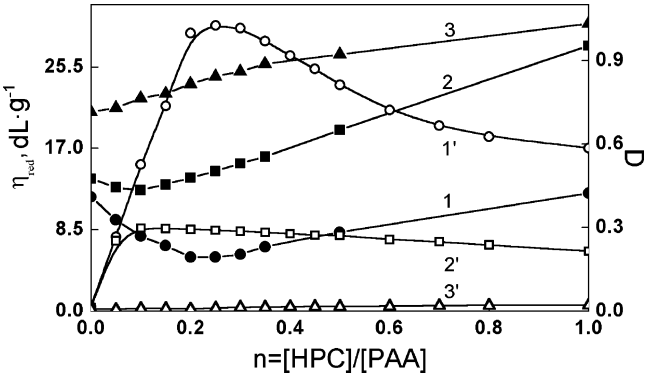

Figure 1. Reduced viscosity (traces 1−3) and optical density (traces 1′−3′) of PAA−HPC aqueous solutions at pH 3.4 (1 and 1′), 3.6 (2 and 2′), and 4.2 (3 and 3′) as a function of the component ratio [HPC]/[PAA]; concentration of polymers 0.01 unit·mol/L, M_w(PAA) = 450 000.

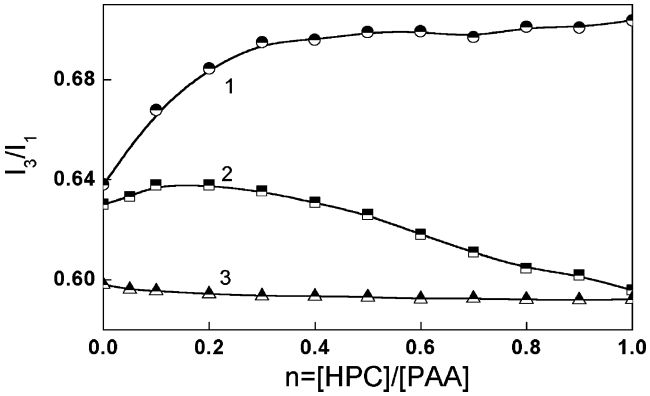

Figure 2. I_3/I_1 ratio of pyrene as a function of [HPC]/[PAA] ratio at pH 3.4 (1), 3.6 (2), and 4.2 (3). Concentration of polymers 0.01 unit·mol/L, M_w(PAA) = 450 000.

presence of any extreme points on the viscosity curve. Addition of HPC to PAA solution is accompanied by an increase in reduced viscosity, which may happen because of the following reasons: (i) a simple dilution of PAA causes unfolding of its macromolecules due to the polyelectrolyte effect; (ii) semirigid HPC macromolecules have quite high viscosity and contribute to the total viscosity of the system; (iii) mixing of PAA and HPC results in formation of a water-soluble associate, which dimensions are larger than the dimensions of individual polymer coils. Completely different trends are observed upon titration of PAA by HPC solutions at lower pH (pH 3.4 and 3.6). Indeed, in this case the mixing of polymers results in appearance of turbidity, which can be observed even by the naked eye. The viscometric titrations also show the presence of extreme points (minima), which correspond to the position of maxima on turbidimetric curves. Initially the addition of HPC to PAA solution leads to formation of compact hydrophobic IPC, which stoichiometry is shown by the position of extreme points on the titration curves. The further addition of HPC results in a decrease of turbidity and increase of viscosity due to the presence of excessive uncomplexed macromolecules in the system. It should be noted that the stoichiometry of IPC is pH-dependent. The ratio of PAA/HPC in the complex formed at pH 3.4 is 4:1 unit·mol, whereas at pH 3.6 it reaches 10:1 unit·mol. Similar pH-dependent IPC stoichiometry was previously reported by Ikawa et al.[15] for complexes of PAA and poly(ethylene oxide) (PEO) and was explained by the different number of un-ionized carboxylic groups of PAA able to form H-bonds. However, unlike PEO and many other complexes of PAA with synthetic nonionic polymers, the IPC composed of PAA and HPC always result in an excessive amount of the polyacid, which is possibly due to the presence of multiple proton-accepting centers (hydroxyl and ether groups) in every elementary unit of HPC.

To get a deeper insight into the complexation between PAA and HPC, we have applied the fluorescent spectroscopy technique with a pyrene probe. The unique ability of pyrene to migrate to a more hydrophobic environment and change the intensity ratio of the third (383 nm) to the first (373 nm) vibronic peak, I_3/I_1, in its emission spectra makes this technique very powerful for the investigation of complex formation phenomena. However, in most of the studies available in the literature pyrene was covalently attached to one of the interacting polymers, which makes its macromolecules more hydrophobic and enhances their ability to form IPC.[16,17] Previously[18] we reported about the possibility of using free pyrene for the investigation of complex formation via hydrogen bonding. In the present work we applied this technique to monitor the changes in hydrophobic/hydrophilic environment upon mixing PAA and HPC at fixed pH (Figure 2). The I_3/I_1 value for pyrene solubilized in distilled water is around 0.60−0.64.[19,20] The pyrene solubilized in pure PAA solution displays the I_3/I_1 values within this range, and lowering the pH leads to higher I_3/I_1 values. An addition of HPC to PAA at pH 4.2 practically does not change the I_3/I_1 value, indicating that the hydrophilic/hydrophobic balance of the system is not affected by mixing of polymers. This finding can be considered as another example of no complexation in addition to the data of viscometry and turbidimetry. Mixing of PAA and HPC at pH 3.6 increases the I_3/I_1 values slightly until the PAA/HPC ratio reaches 10:1, and then the vibronic peaks ratio decreases again. This increase in I_3/I_1 can be associated with the formation of IPC, which is slightly more hydrophobic than the initial polymers. The mixing of PAA and HPC at pH 3.4 results in a significant increase in I_3/I_1, which may be considered as evidence for the formation of IPC with hydrophobic domains. After the stoichiometry PAA/HPC 4:1 is reached, the I_3/I_1 values come to saturation and do not change significantly. Thus, the results of pyrene fluorescence measurements give the same stoichiometry as the turbidity and viscometry data.

Critical pH of Complexation. Previously we have demonstrated the existence of two different critical pH values (pH_{crit1} and pH_{crit2}) for complexes of poly(acrylic acid) with poly(ethylene oxide)[18]and poly(vinyl alcohol).[21] The mixing of these polymers below pH_{crit1} results in formation of hydrophobic IPC aggregates and their precipitation. The complexes prepared by mixing solutions with pH within the range pH_{crit1}−pH_{crit2} are less hydrophobic and relatively stable to aggregation. Above pH_{crit2} the mixing of polymer solutions does not lead to complexation because the carboxylic groups of PAA are fully ionized and cannot form hydrogen bonds with proton-accepting groups of a nonionic polymer. It can be expected that these observations could represent a general feature of all complexes of poly(carboxylic acids) with nonionic polymers.

The determination of pH_{crit1} and pH_{crit2} values for characterization of the interpolymer complexation between poly(carboxylic acids) and nonionic polymers is important for two reasons: (i) It gives information about the complexation ability of interacting polymers. Higher values of pH_{crit} indicate higher ability of polymer to form IPC. (ii) The pH_{crit1}−pH_{crit2} range is expected to be optimal for casting of homogeneous polymeric films. In the present study we have applied turbidimetric and fluorescent techniques for determination of the critical pH values typical for PAA−HPC complexation. Figure 3 shows the

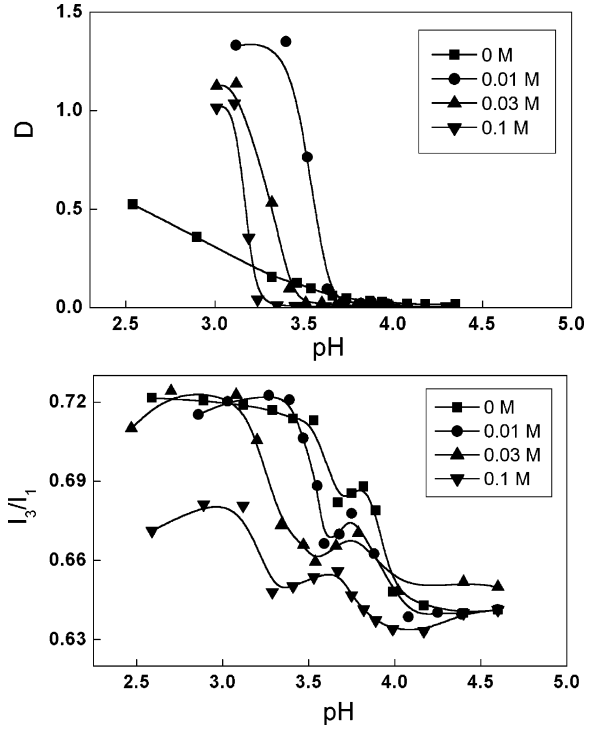

Figure 3. Dependence of optical density (top panel) and pyrene I_3/I_1 ratio of PAA−HPC aqueous mixtures (bottom panel) in the presence of NaCl. The molar concentration of salt in solution is shown in the figure. [PAA] = [HPC] = 0.01 unit·mol.L, M_w(PAA) = 230 000, PAA/HPC = 4:1 mol/mol.

dependence of solution turbidity (top panel) and pyrene vibronic ratios I_3/I_1 (bottom panel) on pH for PAA−HPC solution mixtures in the presence and absence of the inorganic salt NaCl. The experimental curve obtained for salt-free solution shows an increase in turbidity at pH below 3.8, which corresponds to pH_{crit1}. In this case the lowering of pH results in a gradual increase in D; however, in the presence of NaCl the D−pH curves show a significant turbidity increase within a narrow pH interval. The values of pH_{crit1} are shifted to the left upon addition of NaCl, which indicates the unfavorable role of the salt on complexation. The complexation ability of the polymers is decreased in the presence of NaCl due to some ionization of PAA.[22] At the same time the complexation under these conditions is likely to result in larger IPC aggregates giving higher turbidity values. According to our previously published classification,[22] the pH_{crit1} value (pH_{crit1} 3.8) found for PAA−HPC complexes as well as its decrease upon addition of NaCl is an indication of high complexation ability of HPC compared to other nonionic polymers.

The dependence of pyrene vibronic ratio I_3/I_1 on pH displays the presence of two minima, which correspond to pH_{crit1} and pH_{crit2} (Figure 3, bottom). The pH_{crit1} values found by turbidimetric approach (Figure 3, top) and fluorescent approach (Figure 3, bottom) are in good agreement. Below pH_{crit1} the complexes tend to form a hydrophobic aggregate, which is confirmed by the sharp increase in I_3/I_1. The pH_{crit2} values are situated at pH around 4.1−4.2, and these values are not significantly dependent on the presence of the salt. It is believed that between pH_{crit1} and pH_{crit2} the complexes are still formed but they are less hydrophobic and more stable to aggregation. Above pH_{crit2} the formation of IPC is fully disrupted due to significant ionization of PAA and inability of ionized carboxylic groups to form hydrogen bonds.

Miscibility−Immiscibility Transitions in PAA−HPC Solid Films. Solid films were prepared by casting PAA−HPC solution mixtures on polyethylene plates and subsequent evaporation of water on air during several days and drying under vacuum. PAA samples of different molecular weights (2000, 100 000, and 450 000) were used for preparation of polymeric films. The prepared films were preliminarily assessed by measurement of their optical density. Figure 4 shows the dependence of the film's optical density as a function of a casting solution pH. The results show that the films prepared at pH below a certain critical value, which roughly corresponds to pH_{crit2} determined in solutions, remain transparent and have low optical density. The films prepared from solutions with pH higher than the critical pH show a significant increase in optical density, indicating a microphase separation caused by immiscibility of the polymers in a solid blend. The critical pH of the phase separation is a function of PAA molecular weight and it is higher for PAA with longer chain lengths. It is likely that the higher molecular weight of PAA favors the formation of intermolecular hydrogen bonds with HPC due to cooperativity effects. Similar trends with molecular weight are also observed for complexation of polymers in solutions.

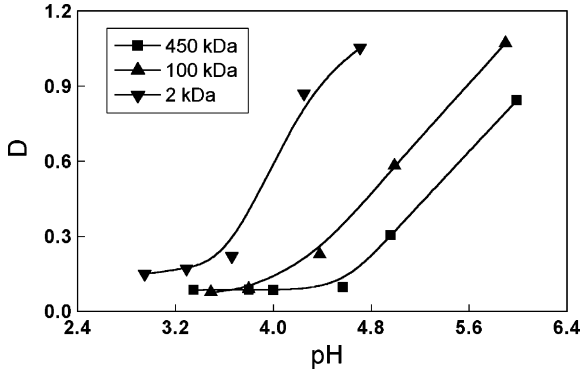

Figure 4. pH effect of casting solution on the optical density of PAA−HPC (1:1 mol/mol) films for PAA samples of different molecular weight.

More detailed information about the morphological properties of the films prepared from solutions with different pH can be obtained by using scanning electron microscopy (SEM) of the sample cross-sections. Figure 5 shows the SEM images of pure PAA, pure HPC, and PAA−HPC films obtained by casting from solutions with pH 3.47, 4.76, and 5.92. The cross-section of pure HPC film has a flakelike morphology, which is quite similar to our previous observations reported for this polymer[14] and is possibly caused by the presence of crystalline domains. Pure PAA film has a homogeneous structure, which is also observed for the PAA−HPC film prepared by casting at pH 3.47. A disappearance of the flakelike morphology typical for pure HPC and homogeneity of this sample indicates the presence of specific interactions between these polymers and proves their miscibility in the blend. The film sample prepared from solution with pH 4.76 shows a rough surface distantly resembling the flakelike morphology of pure HPC. This observation indicates poor miscibility between the component polymers and absence of specific interactions preventing the formation of crystalline domains in HPC. The sample prepared at pH 5.92 shows the presence of two distinct phases: one of the polymers forms spherical structures dispersed in a phase of the second polymer. The polymers are fully immiscible in this blend.

In summary, the pH of polymer solutions used for casting affects the possibility of the film's formation and the miscibility of the polymers in a solid blend significantly. The reason of these pH effects is the variation in the strength of hydrogen bonding occurring between PAA and HPC. When the pH of

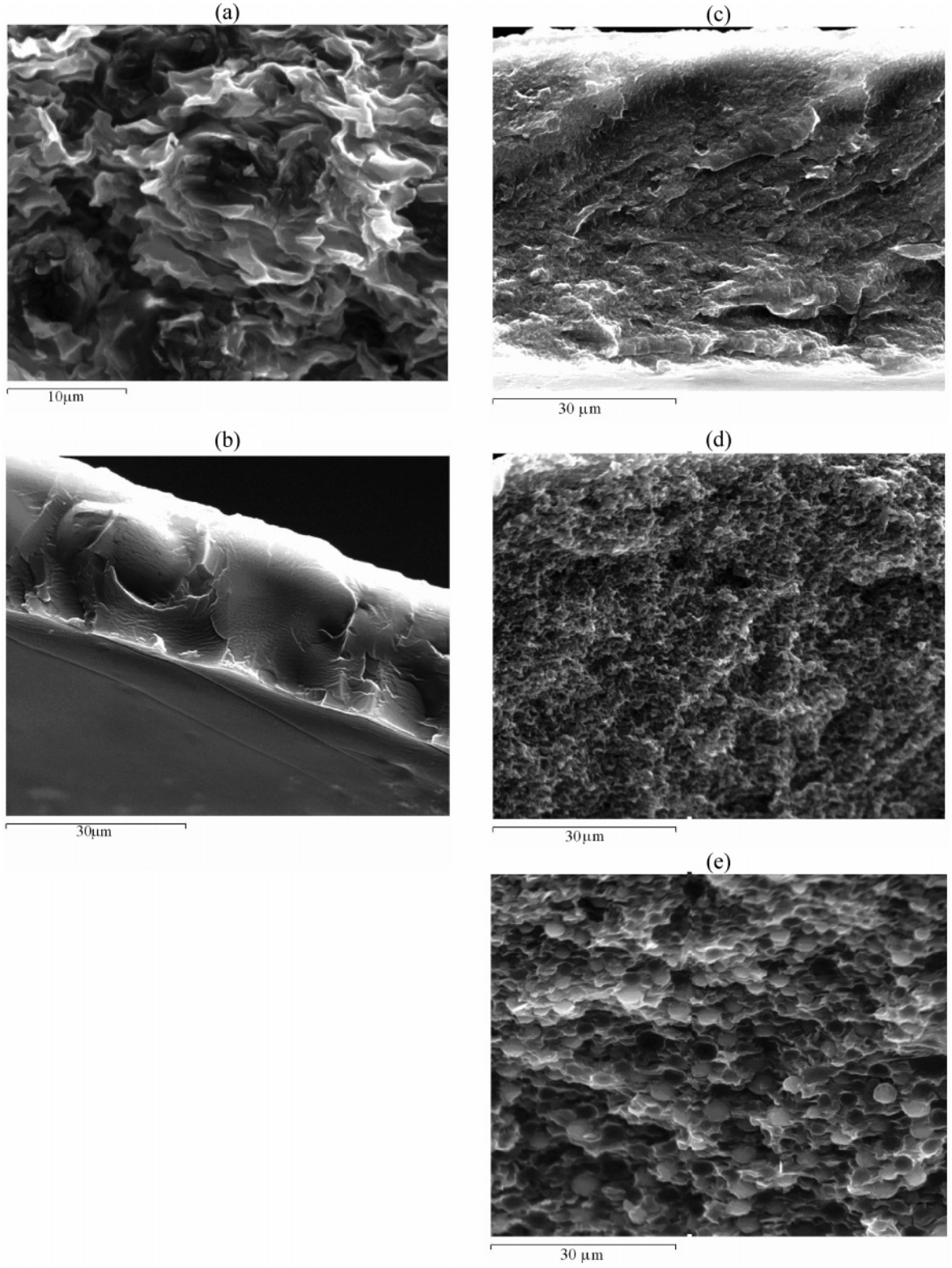

Figure 5. SEM images of pure HPC (a), pure PAA (b), and PAA−HPC (1:1 mol/mol) films (c−e) cross-sections. pH of the casting solution was 3.47 (a, c), 4.76 (b, d), or 5.92 (e). M_w(PAA) = 450 000.

solutions is below pH_{crit1} for a given polymer concentration, the mixing results in precipitation of IPC, which is unfavorable for casting of films. When the solution pH is high enough and the interpolymer hydrogen bonding between PAA and HPC is completely prevented (above pH_{crit2}), the polymers are fully immiscible in a solid blend and the resulting film is inhomogeneous, turbid, and brittle. The homogeneous films can be prepared only by casting from polymer solutions, where the pH is within the $pH_{crit1}-pH_{crit2}$ range.

Radiation Cross-Linking and Swelling Properties of PAA−HPC Films. The properties of polymeric films composed of water-soluble polymers can be modified by cross-linking, which results in formation of insoluble materials able to swell in water and form hydrogels. The application of ionizing

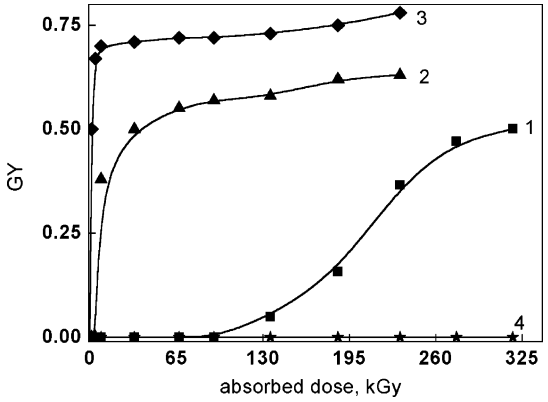

Figure 6. Effect of absorbed dose on the gel yield (GY) of PAA (traces 1−3) and HPC (trace 4) films. Cross-linking agent was present at 0.2 (1), 0.5 (2), or 1 mol % (3, 4); M_w(PAA) = 450 000.

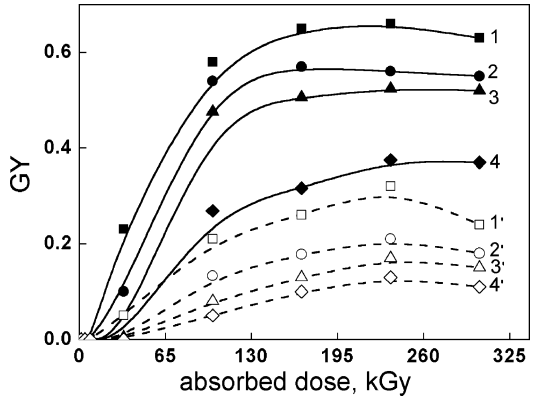

Figure 7. Effect of absorbed dose on the gel-fraction yield of PAA−HPC films. Cross-linking agent was present at 0.2 mol % (traces 1′−4′) or 0.5 mol % (traces 1−4); PAA/HPC = 70:30 (1, 1′), 60:40 (2, 2′), 50:50 (3, 3′), or 40:60 mol % (4, 4′). M_w(PAA) = 450 000.

radiation has been widely employed for production of hydrogels and biomaterials because of a number of advantages compared to the other cross-linking methods.[23]

The efficiency of polymer cross-linking upon irradiation depends on the structure of macromolecules, the state of the irradiated system (solution or dry state), and parameters of radiation. Cross-linking and chain scission normally proceed simultaneously, but the most prevalent process determines the outcome of irradiation treatment.[24] The γ-irradiation of dry films composed of pure PAA and HPC has resulted in gel formation only for PAA (Figure 6) because polysaccharides usually undergo chain scission.[25] We attempted to facilitate cross-linking by adding different amounts of *N*,*N*′-methylenebis(acrylamide) (BAA) to the polymer solutions used for the film casting. This resulted in significant improvement of the cross-linking efficiency for PAA but was inefficient for HPC films.

γ-Irradiation treatment of the films composed of PAA−HPC blends did not lead to the formation of gels, which is likely because of the domination of the chain scission process over cross-linking. However, the presence of BAA in the dry blends facilitated their cross-linking significantly. Figure 7 shows the gel yield (GY) values as a function of absorbed dose for the films composed of PAA and HPC. Irradiation of the films containing 0.2 mol % BAA for up to 235 kGy results in an increase of the gel yield. The further increase in absorbed dose leads to some lowering of the GY values. It is likely that under these irradiation conditions the role of chain scission becomes more significant, which lowers the cross-linking efficiency at higher doses. The cross-linking of the films containing 0.5 mol

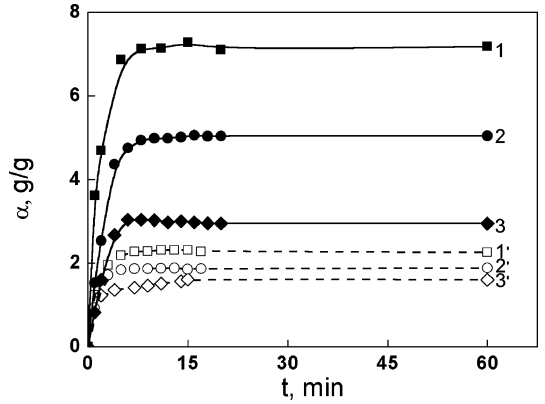

Figure 8. Swelling kinetics of radiation cross-linked PAA−HPC films in aqueous buffer solutions with pH 1.68 (traces 1′−3′) and 6.86 (traces 1−3). PAA/HPC = 60:40 (1, 1′), 50:50 (2, 2′), or 40:60 mol % (3, 3′); cross-linking agent was present at 1 mol %, absorbed dose 100 kGy, ionic strength 0.2, M_w(PAA) = 450 000.

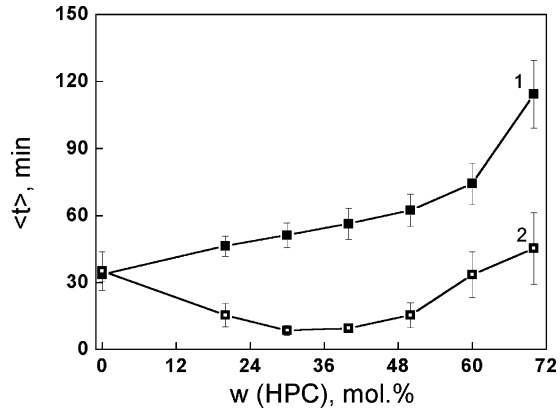

Figure 9. Mucoadhesion of soluble (1) and cross-linked PAA−HPC films (2) in aqueous buffer solutions with pH 6.86. PAA/HPC 1:1 mol/mol, M_w(PAA) = 450 000, cross-linking agent was present at 0.5 mol %, absorbed dose 100 kGy, ionic strength 0.2.

% BAA is more efficient and is not accompanied by a decrease in GY for absorbed doses up to 302 kGy. The blends containing higher amounts of PAA can be more easily cross-linked and give larger GY values.

The swelling properties of the cross-linked films have been examined in buffer solutions with pH 1.68 and 6.86. Figure 8 shows that in both cases the films reach equilibrium swelling within 8−15 min. The swelling degrees determined for the samples at pH 6.86 are significantly higher than those obtained at pH 1.68, which is likely to be due to the high ionization degree of PAA at pH 6.86. Also at pH 1.68 the formation of intermacromolecular hydrogen bonds between PAA and HPC is possible, which act as additional physical cross-links, decreasing the swelling degree of the films. The samples containing larger amounts of PAA show higher swelling degrees even at pH 1.68, confirming higher hydrophilicity of PAA compared to HPC.

Mucoadhesive Properties of PAA−HPC Films. Mucoadhesive properties of both soluble and cross-linked PAA−HPC films with respect to freshly excised porcine buccal mucosa were assessed by a procedure similar to the previously described "rotating disk method".[26] The film samples were wetted and placed into contact with mucosal tissue attached to a rotating disk, which was immersed into buffer solution with pH 6.86.

Figure 9 shows the results obtained for both cross-linked and un-cross-linked films. Dissolution of un-cross-linked PAA−HPC films adhered to mucosal tissue is observed within 30−110 min

depending on the polymer ratio. An increase in HPC content in the film results in slower dissolution, which is possibly due to the poorer hydrophilic properties and higher rigidity of HPC macromolecules. The cross-linked films based on pure PAA detached within 30−35 min, which is very close to the dissolution time observed for un-cross-linked samples. It indicates that the mucoadhesion of pure PAA is mostly related to its hydrogen bonding with the mucus layer, and the diffusion/entanglement mechanism plays a less important role. However, the films composed of cross-linked PAA−HPC blends retained onto the mucosal tissue surface for significantly shorter periods of time compared to the dissolution of the un-cross-linked materials (10−40 min). This can be related to a significant contribution of the macromolecules' diffusion and chain entanglement into mucoadhesion. The detachment of cross-linked PAA−HPC blends is also a function of the blend composition. An increase in HPC content in the blend of up to 30−35 mol % results in the lowering of a mucoadhesive potential of the formulation. The further addition of HPC up to 70 mol % leads to improvement of mucoadhesive properties, reaching the values of detachment time typical for the films composed of pure PAA.

Conclusions

An understanding of specific interactions between polymers can help in design of polymeric materials with required properties. In the present study we have demonstrated that analysis of the factors affecting the complexation between poly(acrylic acid) and (hydroxypropyl)cellulose in aqueous solutions can be used to find out the specific conditions necessary for preparation of homogeneous polymeric films. The miscible films can be prepared by casting polymer solution mixtures at the pH, which is between the critical pH values (pH_{crit1} and pH_{crit2}), observed for the complexation of poly(acrylic acid) and (hydroxypropyl)cellulose.

The properties of the polymeric blends can be altered significantly by ionizing irradiation treatment. The PAA−HPC blends undergo chain scission upon irradiation, but this process can be reversed by addition of *N*,*N*′-methylenebis(acrylamide) as a cross-linker. An immersion of cross-linked films in water results in formation of hydrogel films, which reach equilibrium swelling within 8−15 min.

The soluble and cross-linked films have completely different properties when attached to buccal mucosa. Soluble films adhered to mucosal tissues undergo dissolution within 30−110 min depending on the polymer ratio in the blend. Cross-linked films are retained on mucosal surface for 10−40 min and then detach. It is believed that the intermolecular hydrogen bonding, interdiffusion, and chain entanglement are the main mechanisms determining the adhesion of these films to mucosal tissues. The mucoadhesive films prepared in this work may be useful for administration of local anesthetics in dental treatment.

References and Notes

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