Soluble and Crosslinked Hydrophilic Films Based on Compositions of Poly(acrylic acid) and Poly(2-hydroxyethyl vinyl ether) for Controlled Drug Release

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ABSTRACT: Soluble and crosslinked films based on compositions of poly(acrylic acid) and poly(2-hydroxyethyl vinyl ether) were prepared. Solubility, morphology, mechanical characteristics, and swelling properties of the films were investigated. Potential applications of the polymer complex films in controlled drug delivery were also examined. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 90: 137–142, 2003

Key words: hydrogels; poly(vinyl ethers); miscibility; drug delivery systems; irradiation

INTRODUCTION

The mixture of poly(carboxylic acids) with nonionic polymers in aqueous or organic solutions usually results in the formation of interpolymer complexes (IPCs) or miscible blends. IPCs are formed when the carboxylic groups of polyacid are in the protonated state for cooperative intermacromolecular hydrogen bonding with nonionic polymers.[1–5] In aqueous solutions, IPCs are formed as precipitates at pH's below some critical values, which depend on the concentration and nature of polymers,[6–8] the ionic strength of solution[9,10] and the presence of different additives.[10]

The formation of miscible blends between poly(carboxylic acids) and nonionic polymers occurs when the interaction between the two polymers is not so strong as in the case of IPC formation (i.e., a lack of cooperative intermacromolecular hydrogen bonding). The miscible blends of polymers can form homogeneous films.

IPCs and blends of poly(carboxylic acids) with hydroxyl-containing nonionic polymers are useful for the development of different hydrophilic film composite materials[11–14] that can be used for the preparation of novel drug-delivery systems and selective membranes for separation technologies.

In this article, we report the methodology for the preparation of soluble and crosslinked hydrophilic films based on blends of poly(acrylic acid) (PAA) and poly(2-hydroxyethyl vinyl ether) (PHEVE). This study also demonstrated the possibility of using polymer films for the local controlled delivery of the anesthetic lidocaine hydrochloride (Lid · HCl).

EXPERIMENTAL

Materials

PHEVE was synthesized by the γ-irradiation polymerization of 2-hydroxyethyl vinyl ether in bulk with ^{60}Co (MRX-γ-25M) for 9 h at a dose rate of 0.3 Gy/s.[15] The synthesized polymer was purified by precipitation from ethanol to diethyl ether three times and was dried in a vacuum desiccator at 30°C until a constant weight was achieved. The viscosity-average molecular weight (M_v) of PHEVE in water was calculated from the following equation:[16]

$$[\eta] = 8.8 \times 10^{-4} M^{0.50}$$

where $[\eta]$ is intrinsic viscosity. The calculated M_v was 4×10^4 g/mol.

PAA was synthesized by free-radical polymerization in the presence of azoisobutyronitrile. The molecular weight of PAA determined by the viscometric method with the equation $[\eta] = 8.5 \times 10^{-4} M_v^{0.5}$ (in dioxane at 30°C) was 4×10^6 g/mol.

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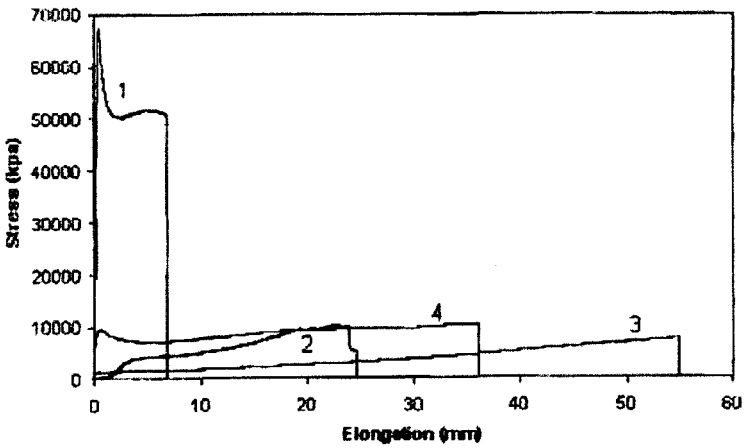


Figure 1 Elongation at stress curves of pure PAA and PAA–PHEVE films. The contents of PHEVE in the films were (1) 0, (2) 20, (3) 40, and (4) 50 mol %.

Lid · HCl was purchased from Khimpharm, Ltd. (Shimkent, Kazakhstan) and was used as received.

Methods

Preparation and crosslinking of the films

We prepared the films by casting aqueous solutions of PHEVE and PAA on a polyethylene surface followed by drying in air.

We crosslinked the films by thermal treatment by heating them in an oven at 90–140°C for the required periods of time. The radiation-induced crosslinking of the films was done with ^{60}Co (MRX-γ-25M) at a dose rate of 0.3 Gy/s.

Measurement of equilibrium swelling

The extent of the equilibrium swelling (α) of the films was determined gravimetrically and was calculated with the formula $\alpha = (m - m_0)/m_0$, where m and m_0 are the weights of the film in the swollen and dry states, respectively.

Mechanical characterization of the films

Membrane samples with the dimensions 20 × 0.75 × 0.103 mm were used for mechanical characterization. The cross-sectional area of the samples was 7.725×10^{-8} m^2.

The mechanical strength of the polymer films was measured with a texture analyzer (Stable Micro Systems by Texture Technologies Corp., Scarsdale, NY). Measurements were made in the tensile force mode at a speed of 2 mm/s for pretest, 1 mm/s for test, and 2 mm/s for posttest.

Scanning electron microscopy (SEM) images

The surface morphology of the polymer films was examined by with a Jeol scanning electron microscope system (model JSM-840, Peabody, MA). Polymer samples were mounted on aluminum stubs and coated with gold–platinum under an argon atmosphere. All samples were scanned at a voltage of 5 kV, a working distance of 28 mm, and an aperture diameter of 50 μm.

Drug release from films

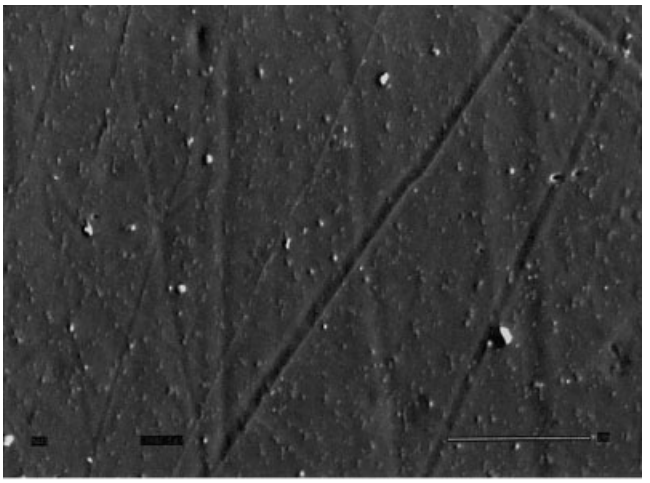
The drug release experiments were conducted in a special diffusion cell with constant stirring. The temperature for the experiments was maintained at 25°C. Aliquots of samples were taken at timed intervals and analyzed with a UV2401PC spectrophotometer (Shimadzu, Japan) at a wavelength of 264 nm.

RESULTS AND DISCUSSION

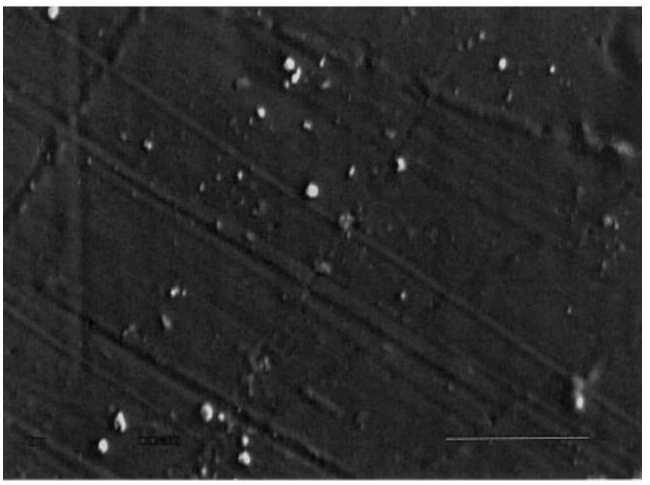
Preparation and characterization of the soluble films

In our previous works,[6,9,11,17] we studied interpolymer interactions between PAA and PHEVE in aqueous and organic solutions to clarify the effects of pH, the ionic strength of the solutions, the polymer concentration, and the nature of the solvent on interpolymer complexation. The formation of IPCs with stoichiometric compositions was demonstrated.

In this work, we prepared the films by casting the aqueous solutions of PAA/PHEVE mixture on a polyethylene surface and drying them in air for several days. Precipitation of IPC was not observed upon mixture of the initial polymer solutions because the pH of the starting solutions was between 5 and 7, which was higher than the critical pH value for this



(a)



(b)

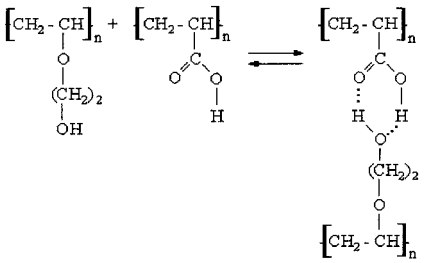
Figure 2 SEM images of (a) pure PAA and (b) PAA–PHEVE (50:50 mol %) films.

system for complex formation.[6,9] The films formed were clear and elastic and possessed moderate adhesiveness to the surfaces.

The mechanical properties of various films were evaluated (Fig. 1). As shown in Figure 1, pure PAA films showed mechanical behavior typical for polymers in the glassy state. The elongation of the film in this state requires considerable stress. The addition of PHEVE to PAA made the material more elastic and increased the elongation to the break point. At higher contents of PHEVE (more than 50 mol %), the film lost its mechanical strength.

To evaluate the miscibility of PAA with PHEVE, the surface morphology of the films was examined with SEM images of the pure PAA [Fig. 2(a)] and PAA–PHEVE (50:50 mol %) films [Fig. 2(b)]. The similar morphology of both samples suggested miscibility between PAA and PHEVE.

The solubility of the films in aqueous media with different pH values was tested. The films were insoluble in buffer solutions with pH values less than 2.5 and were readily soluble at pH values greater than 4. Such behavior could be explained by the formation of insoluble IPCs between PHEVE and PAA in acidic media according to Scheme 1.



Scheme 1

At higher pH values, the intermacromolecular hydrogen bonds were destroyed because the carboxylic groups of PAA were ionized, and thus, the films became water soluble.

Preparation of crosslinked films

To examine the possibility of regulating the properties of the films, we studied the effect of thermal treatment and γ irradiation on their water solubility.

Thermal treatment of the films in an oven with an open atmosphere at 90–140°C resulted in the formation of crosslinked materials that were insoluble but were also able to swell in water to form hydrogels. As shown in Figure 3, an increase in the thermal treatment time led to a decrease of the α of the films in water. Moreover, at higher temperatures, the crosslinking process was more effective. The films were stable during boiling for several hours in 0.1*M* solutions of NaOH or HCl. We previously demonstrated that the crosslinking of these films by heating

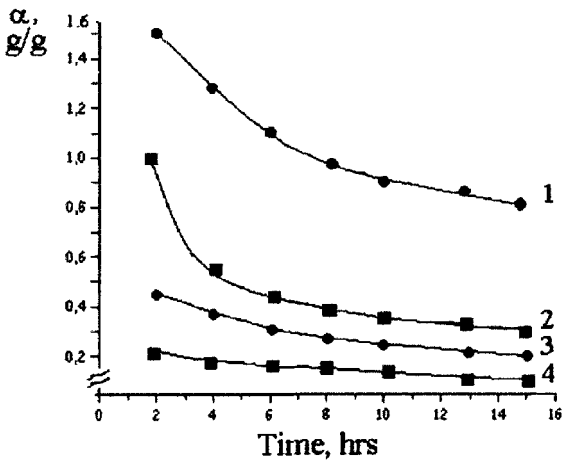
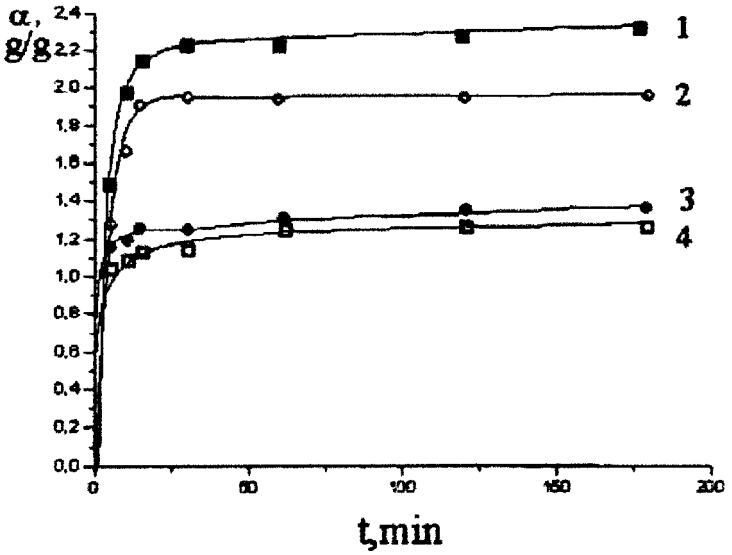
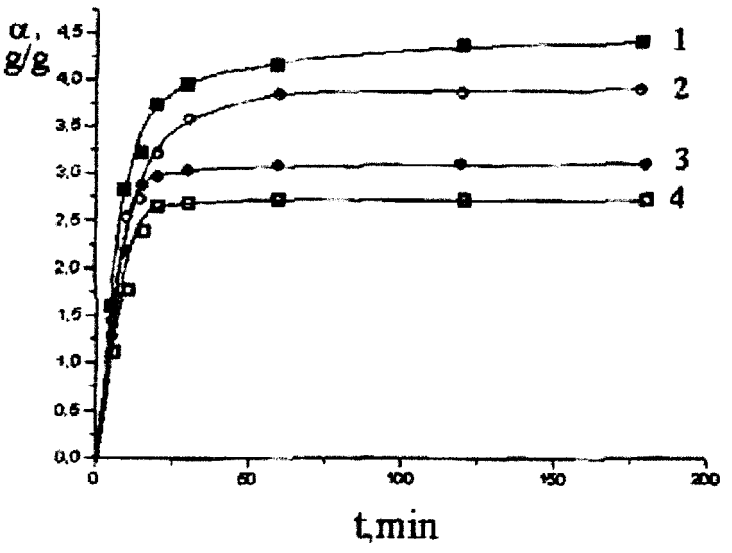


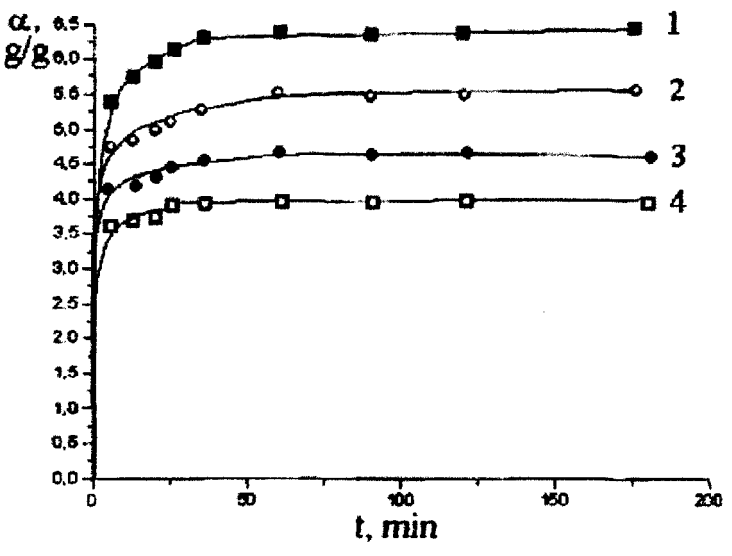
Figure 3 Dependence of α of PAA–PHEVE (1:1) films in water on the thermal treatment time: temperature = (1) 90, (2) 110, (3) 120, and (4) 140°C.



(a)



(b)



(c)

Figure 4 Swelling kinetics of thermally crosslinked PAA–PHEVE (1:1) films in aqueous solutions with different pH values: pH = (a) 3.0, (b) 6.0, and (c) 7.5; thermal treatment time = (1) 4, (2) 6, (3) 8, and (4) 10 h; and temperature = 90°C.

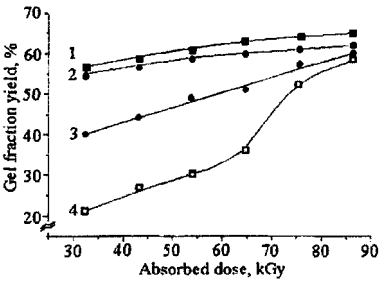


Figure 5 Yield of PAA–PHEVE gels as a function of the absorbed dose of γ radiation: [PAA]:[PHEVE] = (1) 50:50, (2) 60:40, (3) 80:20, and (4) 100:0 mol %.

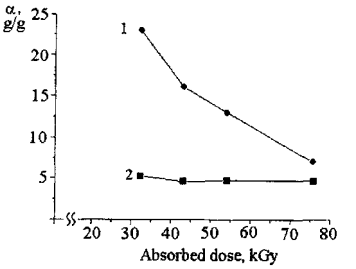


Figure 6 Dependence of α of PAA–PHEVE films in water on the absorbed dose of γ radiation: [PAA]:[PHEVE] = (1) 70:30 and (2) 50:50.

occurs through formation of intermacromolecular ester and ether bonds.[11]

The kinetics of film swelling was studied in aqueous solutions at different pH values [Fig. 4(a–c)]. The films reached the equilibrium swelling state in about 25 min. Relatively low values of equilibrium swelling (1.2–2.3 g of water/1 g of dry polymer) were observed at a pH of 3.0. At higher pH values (e.g., pH = 7.5), the films absorbed larger amounts of water (3.5–6.5 g of water/1 g of dry polymer). This behavior was also related to the formation/dissociation of IPCs in acidic and neutral media.

The radiation crosslinking of polymers provides a number of advantages, such as more homogenous crosslinking of the material and the possibility of sterilization during the crosslinking process. The radiation treatment of dry PAA–PHEVE films resulted in the formation of crosslinked hydrogel materials. The gel yield was plotted as a function of the absorbed dose of γ radiation for PAA–PHEVE films of different component ratios (Fig. 5). An increase in the PHEVE content in the mixture favored the formation of hydrogels at lower absorbed doses.

The dependence of the α of γ-irradiated films on the absorbed dose is plotted in Figure 6. The data on swelling kinetics of irradiated films in distilled water are plotted in Figure 7. A decrease in the swelling ability in water was observed with increasing absorbed dose due to a higher number of intermacromolecular crosslinks formed by γ radiation.

Release of Lid · HCl from the hydrogel films

An oral adhesive film dosage form containing a local anesthetic is useful for the delivery of a drug without pain and first-pass effect in dental analgesia. Okamoto et al.[18] reported the film dosage forms of Lid · HCl based on hydroxypropylcellulose.

The hydrogel films obtained in this study also presented usefulness in the development of the film dosage forms. To evaluate this possibility, we studied the drug-release properties of the films with Lid · HCl (Lid · HCl), an anesthetic drug. It was shown in our previous study[19] that Lid · HCl forms strong complexes with PAA via electrostatic interactions and

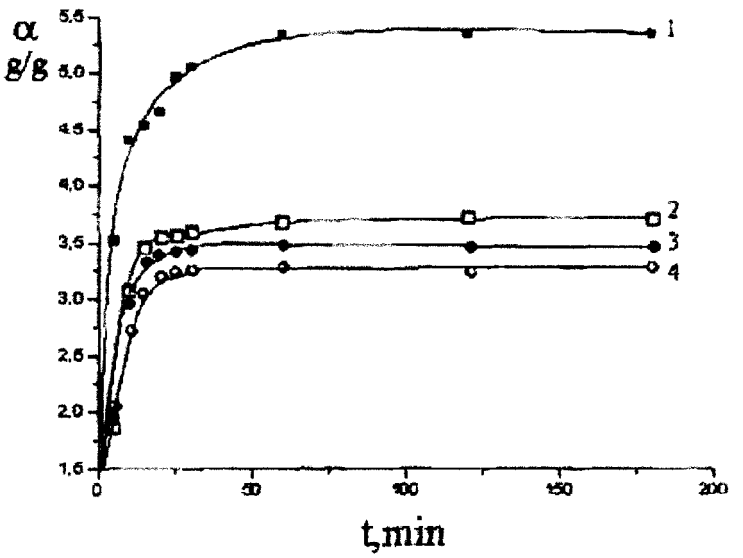


Figure 7 Swelling kinetics of radiation-crosslinked PAA–PHEVE (1:1) films in pure water: absorbed dose = (1) 32.4, (2) 43.2, (3) 54.0, and (4) 75.6 kGy.

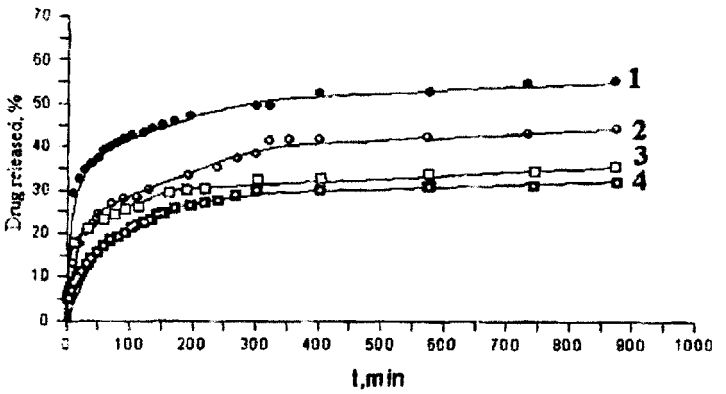


Figure 8 Release of Lid · HCl from the PAA–PHEVE film (irradiated at 32 kGy) into media with different (1–3) pH values and (4) pure water: [PAA] = [PHEVE] = 0.5*M*; [Lid · HCl] = 0.01*M*; and pH = (1) 8.25, (2) 4.05, and (3) 2.0.

weak complexes with PHEVE via hydrogen bonding and hydrophobic interactions.

The films loaded with Lid · HCl were prepared by the mixture of aqueous solutions with 10 mL of 0.5*M* PAA, 10 mL of 0.5*M* PHEVE, and 2 mL of 0.01*M* Lid · HCl, followed by drying in air and γ irradiation at an absorbed dose of 32 kGy.

The amount of lidocaine released from each film was measured by an ultraviolet spectroscopic technique. Figure 8 shows the results of Lid · HCl release from PAA–PHEVE films into aqueous solutions at different pH values. The loading of Lid · HCl into PAA–PHEVE films resulted in sustained release after an initial burst release. The Lid · HCl release was fastest in the medium with a pH of 8.25, and in these conditions, about 50% of the drug was released during the first 10 h. At more acidic pH values, the release of the drug was slower, which was probably due to the lower swelling extent of the films. In pure water, the release was the slowest, and this was probably related to the low ionic strength of the solution. A higher ionic strength favored the dissociation of complexes between the drug and polymer due to charge shielding effects. A considerable portion of the drug still remained inside the films even after 14 h of release, and this was most likely due to the strong electrostatic interactions of Lid · HCl with free carboxylic groups of the film polymers.

CONCLUSIONS

Water-soluble films based on PAA and PHEVE were prepared by casting techniques. The solubility of the films was affected by the pH of the aqueous solutions and was determined by the formation/dissociation of IPCs between component polymers. SEM observation and mechanical analysis of the films confirmed the miscibility between the component polymers. An increase in the PHEVE content in the film in the 10–50% range made the films more elastic.

Films crosslinked by thermal treatment or γ irradiation were studied. The swelling behavior of the crosslinked materials in aqueous solutions at different pH values was evaluated, and the release of Lid · HCl from the films was also examined. The prepared films were of considerable interest for the development of drug-delivery systems.

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