Immobilization of 2,5-Dimethyl-4-benzoyl-oxypiperidine Succinate over Polyacrylic Acid (PAA) Gels. I. Study of Interaction Between Linear and Network PAA with Succinate of 2,5-Dimethyl-4-benzoyl-oxypiperidine

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ABSTRACT: The interaction of water-soluble and crosslinked polyacrylic acid (PAA) with a medicinal compound (MC) of 2,5-dimethyl-4-benzoyl-oxypiperidine succinate was investigated. By methods of potentiometry, viscosimetry, and equilibrium swelling it was confirmed that the interaction of linear and network PAA with MC proceeds with complex formation. The degree of complex formation depends on the effect of pH, MC concentration, and degree of polyacid crosslinking. © 2005 Wiley Periodicals, Inc. J Appl Polym Sci 96: 1183–1186, 2005

Key words: hydrogels; swelling; crosslinking; drug delivery systems; networks

INTRODUCTION

Recently polymer hydrogels have been widely used for the creation of new polymeric forms of medicines. They are able to absorb extremely large quantities of both water and aqueous solutions and to reversibly change their parameters under the action of weak alterations of medium (pH, ionic force, temperature, etc.).[1–3] Polymer hydrogels are used for immobilization of enzymes, isolation and cleaning of biologically active compounds, and controlled separation and purposeful transportation of medicines. For immobilization of medicinal compounds the water-soluble and network polyacrylic acid (PAA) is an attractive polymer among synthetic materials because PAA is a water-soluble, nontoxic, and biocompatible compound. Moreover, PAA is able to form complexes with many high- and low-molecular compounds. Therefore we decided to investigate the interaction of polyacrylic acid gels (PAAG) with succinate of 2,5-dimethyl-4-benzoyl-oxypiperidine (AK-29), which has important anaesthetic and analgesic properties.

EXPERIMENTAL

Polyacrylic acid (PAA) was prepared by polymerization of acrylic acid in a solution of dioxane at 70°C in the presence of benzoyl peroxide (0.5% from weight of monomer), and then was purified by overprecipitation from dioxane into petroleum–ether. The fraction with a molecular weight of 1.2×10^5 was used.

The polyacrylic acid gel (PAAG) was prepared by radical polymerization in 10% aqueous solution at 70°C in the presence of dinitrile–azobisisobutyric acid (DAA) as an initiator (0.5% from monomer weight). Methylene-bis-acrylamide (MBAA) was used as a crosslinking agent. Polymerization was carried out for 1 h. The obtained gel was washed from the unreacted monomers with water. The completeness of washing was controlled by a qualitative reaction with $KMnO_4$.

Succinate of 2,5-dimethyl-4-benzoyl-oxypiperidine (AK-29) was synthesized by the faculty members of the departments of organic chemistry and chemistry of natural compounds and was made available for use in our studies (T_{melt} = 150–151°C).

Potentiometric titration of a PAA solution with the AK-29 solution was carried out in a thermostatic glass cell by an EV-74 ion meter, equipped with glass and chlorine–silver electrodes. The experimental temperature was established with an accuracy of ±0.1°C. Experiments were carried out with constant mixing of solutions. The accuracy of pH measurements was ±0.05.

The reduced viscosity of PAA solutions was measured by a Ubbelohde viscometer with a suspended level of liquid (time of dissolvent effusion ~ 194 s). The accuracy of temperature and reduced viscosity (η_{red}) were ±0.1°C and ±1%, respectively.

The degree of gel swelling (α) was determined by the method of equilibrium swelling and was calcu-

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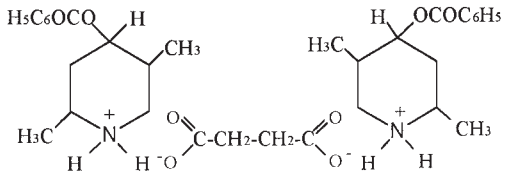

Scheme 1

lated as the ratio between masses of swelled and dry samples:

$$\alpha = \frac{m - m_0}{m_0}$$

where m is the mass of dry sample and m_0 is the mass of the swelled sample.

RESULTS AND DISCUSSION

Complex formation between water-soluble PAA and AK-29

It has been established[4] that weakly crosslinked polyelectrolytes during complex formation, with oppositely charged low-molecular compounds, exhibit behavior like that of their water-soluble analogues, although network polymers can show a significantly high inclination and specificity to complex formation compared with that of their linear analogues.[5] This explains why the viscosimetric and potentiometric investigations of binding between AK-29 and linear PAA were carried out to elucidate the mechanism of interaction between PAAG and AK-29.

The data of viscosimetric and potentiometric titration of PAA with a solution of AK-29 are presented in Figure 1. Results show that the significant increase of the system's reduced viscosity is observed upon addition of a low content of medicinal compound to the aqueous solution of PAA ($n \leq 0.2$). A further increase of n (n = [AK - 29]/[polyacrylic acid]) causes a slow decrease of viscosity compared with the titration by the physiological solution. The minimum value was reached at $n \approx 1.0$. Upon potentiometric titration of PAA solution, by solution of the medicinal compound (curve 4), a slighter pH increase was observed compared with that of water. It is noteworthy that the maximum pH values for the PAA–AK-29 system are significantly less than those for the water–AK-29 system. Such behavior of polymer acid upon mixing with AK-29 together with the extreme character of the curves indicate complex formation. On the assumption of the curve character and increases of both viscosity and pH, the complex formation occurred primarily because of the hydrophobic interactions and intermolecular hydrogen bonds.[6] As a result, the polyelectrolytic chain obtains an additional charge caused by macromolecular unwrapping.[7] Obviously, the decrease in reduced viscosity at $n > 0.2$ may be explained by the contribution of the electrostatic interaction, decreased density of the chain charge, and also by an increase of ionic force attributed to the growth of AK-29 concentration. The relatively smaller contribution of electrostatic interactions is probably caused by the rather weak basicity and polarity of the quaternary ammonium compound of AK-29.

It should be noted that the system remains water soluble at all studied n values, which indicates the main contribution of both hydrophobic interactions and hydrogen bonds to the complex formation.

The dependency of the reduced viscosity of PAA and the PAA–AK-29 blend on pH is the additional evidence of that. Figure 2 shows that curves showing the dependency of $\eta_{op}^{red} = f(\text{pH})$ have maxima that correspond to the field of maximum ionization and unwrapping of macromolecular chains. The increase of AK-29 quantity in the system results in a decrease of viscosity attributed to complex formation. It is interesting to note the appearance of two maxima at high values of n (curves 3 and 4), indicating the polyampholitic character of complexes in this field.[3] These maxima probably correspond to the basic (pH = 9–10) and acid (pH ≈ 6.0) fields of the forming complexes. Obviously, the carboxylic groups of polyacid and quaternary nitrogen of AK-29 give the acidity and basicity to the polycomplex, respectively, thus proving the predominant role of noncoulombic forces of interactions upon binding of medicinal compounds with PAA.

Interaction of medicinal compound over network PAA

An important property of polymer gels is their turgescence.[3,5] Figure 3 shows that the volumes of PAAG,

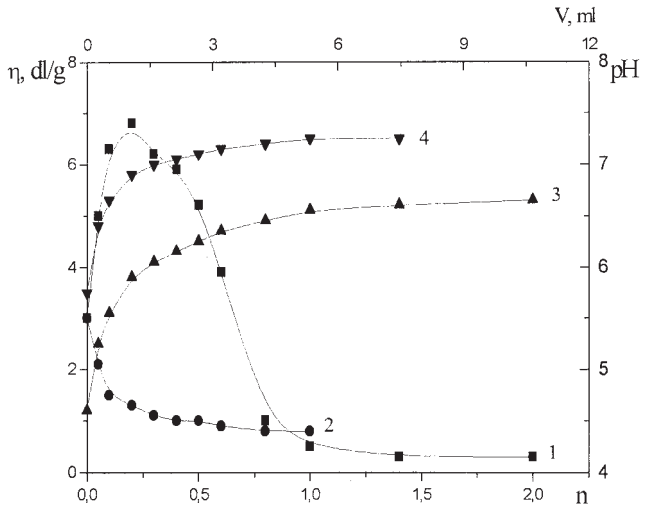

Figure 1 Curves of viscosimetric (1, 2) and potentiometric titration (1, 2) of PAA (1–3) and water (4) with the solutions of AK-29 (1, 3, 4) and of NaCl (2). [PAA] = 0.01*M*; [AK-29] = 0.01*M*; [NaCl] = 0.01*M*.

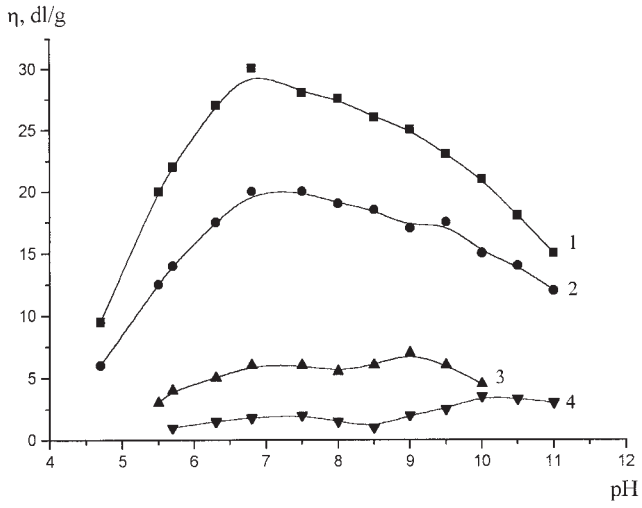

Figure 2 Dependency of the reduced viscosity of PAA (1) and PAA–AK-29 blend (2–4) on pH at n values of 0.1 (2), 0.5 (3), and 1.0 (4), where n = [AK-29]/[PAA].

upon their submergence in water or solutions with various concentrations of AK-29, are significantly increased and reached the equilibrium value after 1 h. The tendency to a monotonous increase is observed. The degree of PAAG swelling increases with increasing medicinal compound concentration upto 1×10^{-4} M (Figs. 3–5). It parallels the analogous dependency of the reduced viscosity for water-soluble polyacid (Fig. 4). Such behavior shown by network polymer can be explained by the binding of the low-molecular compound, attributed to the hydrogen bonds, and hydrophobic interactions, resulting in the increase of gel charge density. The same results were obtained earlier[5,8] in studies of interactions of ionogenic crosslinked and

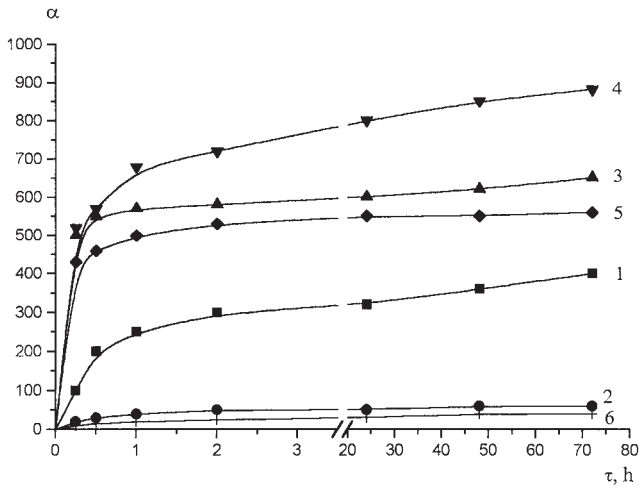

Figure 3 Kinetics of PAAG swelling with 0.1 mol% MBAA content in water (1), physiological solution (2), and solutions of AK-29 with concentrations of (in M): (3) 5×10^{-5}, (4) 1×10^{-4}, (5) 1×10^{-3}, and (6) 1×10^{-2}.

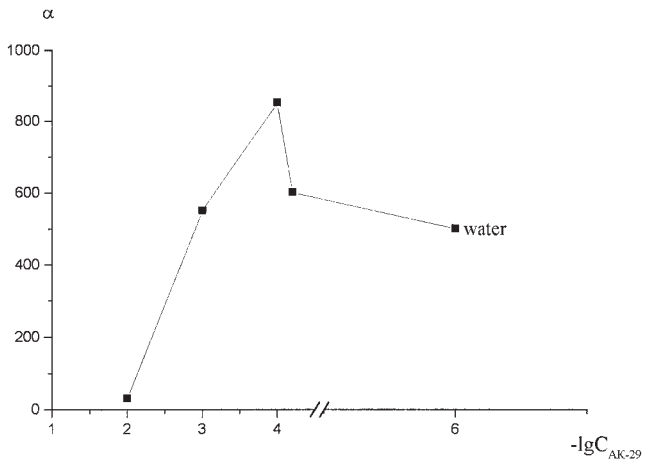

Figure 4 Concentration dependency of PAAG swelling with 0.1 mol % MBAA content. Swelling time: 2 days.

non-ionogenic linear polymers. Additional swelling of the network polymer can be attributed to the increase of charge density in the near-surface layer attributed to complex formation.

Upon further increase of AK-29 concentration the decrease in gel size is observed (Figs. 3 and 4), caused by an increase of the ionic force attributed to an increase of the AK-29 concentration and compression of macromolecular network as a result of the ionic screening of charged functional groups.[9] The maximum compression of gel occurred under the action of the ionic force in physiological and AK-29 solutions with a concentration of 10^{-2} M: the corresponding curves of gel swelling provide evidence of that.

The same results were obtained in the study of PAAG turgescence with the highest content of crosslinking agent (0.25 mol %) (Fig. 5). The increase of content of crosslinking agent in the gel leads to a decrease in swelling degree, which can be explained by the decrease of gel pore size, resulting in a decrease of chain flexibility.[4]

It is known that ionization and the conformational state of macromolecules depend on pH.[10] In particular, if the decrease of pH leads to a suppression of ionization of the polyacid carboxylic groups and compression of macromolecular coils, then with increasing pH, the ionization and unwrapping of the polyelectrolytic chain occur. In fact, as shown in Figure 6, the significant increase of the degree of gel swelling in water is observed with increasing pH. It should be noted that in the case of water-soluble PAA the maximum unwrapping occurred at neutral pH values, whereas the maximum unwrapping of the crosslinked analogue shifted into the basic field, probably attributable to the presence of a spatial structure that makes difficult the ionization of carboxylic groups in the gel phase. Under conditions of pH variation, the turgescence of the polyelectrolytic network in an AK-29

solution passes through a maximum at pH = 7–9. The further alkalization of the medium leads to its monotonous decrease, although in the acidic region (pH ≤ 7) the swelling values of the PAA–AK-29 system is significantly higher than that of the gel. Such limits of gel sizes may be explained by complex formation as well as by the polyampholytic character of the formed complexes.[3]

CONCLUSIONS

The mechanism of interactions of PAA gels with AK-29 medicinal compound was investigated.

It has been established that, upon the interaction between AK-29 and linear and network PAA, the complex is formed mainly because of the hydrophobic and intermolecular hydrogen bonds.

The degree of complex formation and properties of the polymer–MC complex depend on the medicinal compound concentration, pH, and content of crosslinking agent in the gel.

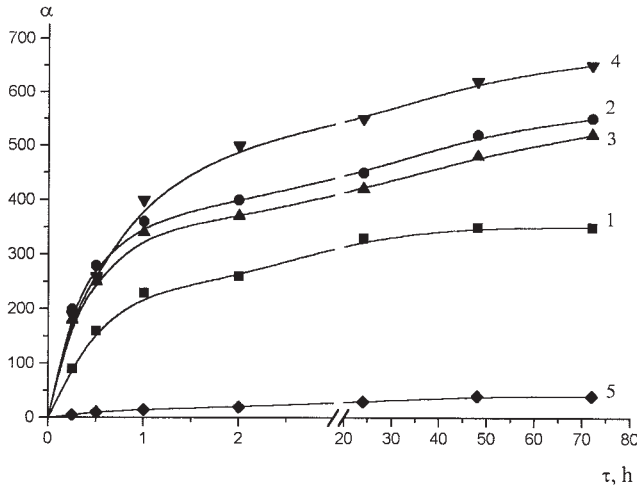

Figure 5 Kinetics of PAAG swelling with 0.25 mol% MBAA content in water (1), physiological solution (5), and solutions of AK-29 with concentrations of (in *M*): (2) 5×10^{-5}, (3) 1×10^{-4}, and (4) 1×10^{-3}.

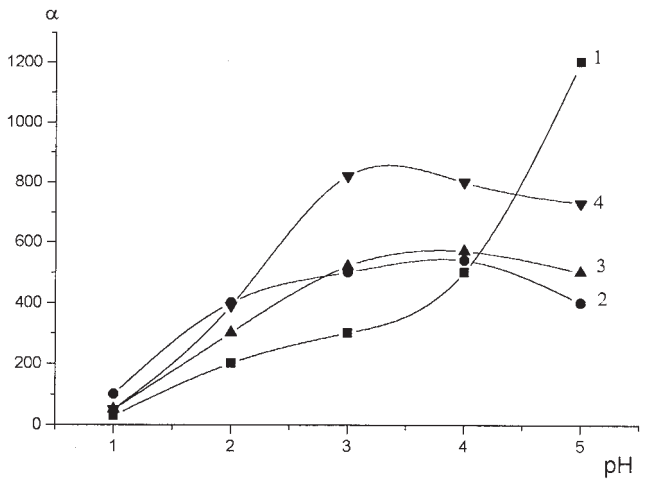

Figure 6 Dependency of degree of PAAG swelling (1) and PAAG–AK-29 (2–4) on pH at *n* values of 0.06 (2), 0.12 (3), and 0.52 (4). MBAA content is 0.25 mol %.

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