Interaction of a New Anesthetic Drug Richlocain with Linear and Weakly Crosslinked Poly-*N*-vinylpyrrolidone

G. Sh. Makysh,[1] L. A. Bimendina,[1] K. B. Murzagulova,[2] S. E. Kudaibergenov[1]

[1]*Institute of Polymer Materials and Technology, Satpaev Str. 18a, 480013, Almaty, Kazakhstan*
[2]*Pharmaceutical Company "Romat", Kamzin Str. 33, 637046, Pavlodar, Kazakhstan*

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ABSTRACT: The properties of complexes of richlocain, a new local anesthetic drug, with linear and weakly crosslinked poly-*N*-vinylpyrrolidone were investigated with changes in media properties of pH, temperature, and solvent thermodynamic quality. The kinetics and activation energy of drug release from the gel matrix were determined.
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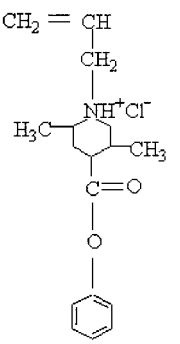
Key words: association; solution properties

INTRODUCTION

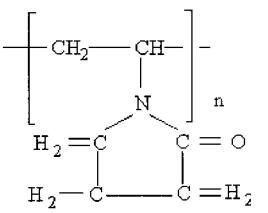
Practical medicine is in need of more rational methods of introduction of drugs into the organism and, therefore, the prolongation of the action of a drug by binding with a polymer carrier is of great interest and attracts the attention of different specialists.[1–4] Poly-*N*-vinylpyrrolidone is one such polymer carrier that is water soluble and widely used in medicine and pharmaceutics because of its lack of toxicity and high ability to form complexes.

Richlocain is a new local anesthetic drug, invented by Kazakh chemists, that has been registered and approved for use in CIS countries.[5] In medicine, richlocain is applied only as an isotonic injection solution. In this form, richlocain has a short duration of action and must be applied repeatedly for pain of long duration. Development of a new drug dosage form with prolonged duration action would be beneficial.

The purpose of the research presented here was to investigate the interactions of richlocain (drug) with linear (LPVP) and weakly crosslinked (GPVP) poly-*N*-vinylpyrrolidone as they relate to the manufacture of a prolonged-release dosage form of this drug (see structures).



Richlocain



Monomer link of LPVP and GPVP

EXPERIMENTAL

Materials

Richlocain (drug), a commercial product of "Asfarma" Ltd. (, Russia), was used without the purification. The maximum absorption of drug is observed at $\lambda = 275$ nm[5]. Linear poly-*N*-vinylpyrrolidone (LPVP), with weight average molecular weight (M_w) of 350×10^3 was purchased from "Serva" (, Germany) and used without purification. Weakly crosslinked, water-swelling poly-*N*-vinylpyrrolidone (GPVP-1) was synthesized at the Institute of Applied Radiation Chemistry of Technical University of Lodz (Poland) by γ-irradiation polymerization in the presence of crosslinking agent at room temperature. GPVP-1 is a commercial product. A sample of this hydrogel was dried to constant weight. The swelling coefficient (K_S) of GPVP-1, determined gravimetrically as mass of water per gram of dried gel, is 20 g/g. The second sample

Correspondence to: L. A. Bimendina (farmz@nursat.kz).

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of crosslinked poly-*N*-vinylpyrrolidone (GPVP-2) is also commercial product (, Germany), with K_S = 7.0 g/g in water. All solvents were reagent grade, and all measurements were carried out in distilled water (pH = 7.0).

Instrumentation

Potentiometric and conductimetric titrations were carried out on a pH/conductivity meter (Mettler Toledo MPC 227, , Sweden) at room temperature. The concentration of immobilized drug in the gel matrix was determined by measuring the optical density of the supernatant at at λ = 275 nm with an SF-16 spectrophotometer (Russia). GPVP-1 was found to bind 15% of the drug.

Methods

LPVP–drug complexes were obtained by mixing aqueous solutions of interacting components in defined ratios. Concentrations are expressed as the masses of corresponding substances. Gel–drug complexes were obtained by immersing swollen gels in aqueous solutions of drug of defined concentration. The gel–drug complexes were equilibrated for 3 h, separated from solution, dried in vacuum at room temperature, and ground to a powder consistency.

Investigation of the kinetics (sorption or desorption) of the drug was carried out by determining the drug concentration in the supernatant at certain time intervals by measuring optical density at λ = 75 nm. The swelling coefficients (K_S) of gel and gel–drug complexes were determined gravimetrically and are expressed as mass of water per 1 g of dried gel. In accordance with kinetic investigation results, the time of gel equilibrium swelling is 2 h. Swelling coefficients of gels in the presence of the drug were determined up to 3 h in all experiments. The viscosity of the solutions was measured with an Ubbelohde viscometer.

RESULTS AND DISCUSSION

The short duration of action of richlocain created the need to investigate the creation of polymer forms of the drug that would possess a prolonged duration of action. These investigations were developed by academician B.A. Zhubanov and collaborators, who studied linear, water-soluble methylcellulose, Na-carboxymethylcellulose, and poly-*N*-vinylpyrrolidone,[6] polymer carriers that are biocompatible and frequently used in medicine. These authors showed that use of these polymers as carriers for richlocain increases the duration of action of this anesthetic drug and maintains a sufficient drug concentration in the recipient organism.[6]

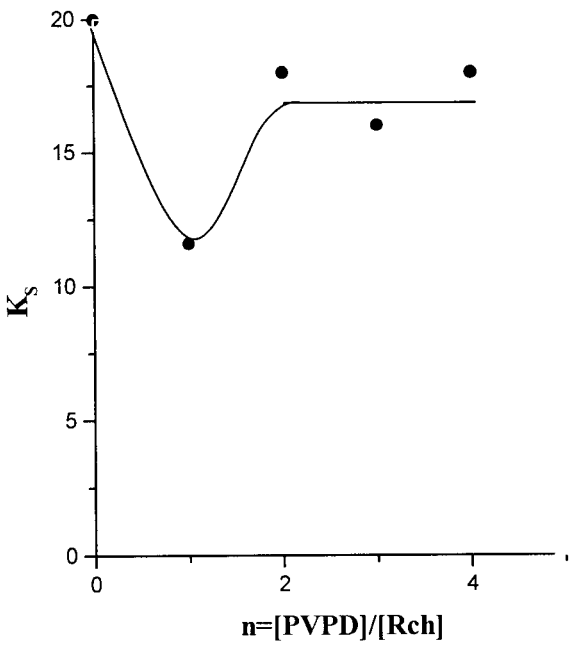

Figure 1 Dependence of swelling coefficients K_S of GPVP-1 on the logarithm of drug concentration.

In a previous publication, we reported the use of weakly crosslinked, charged polymers (hydrogels) of sodium polyacrylate and betain-type polyampholyte, based on acrylic acid and ethyl ether of aminocrotonik acid, for immobilization of richlocain.[7] The binding was realized through electrostatic interactions of positively charged drug richlocain and negatively charged matrix. In the present work, GPVP (a hydrogel of PVP) was used as the polymer carrier. It this case, one can assume that binding would be realized by hydrophobic interactions because PVP is the most hydrophobic of water-soluble nonionic polymers. Furthermore, the chemical composition of PVP is close to that of polyleicine, which is a typical hydrophobic polypeptide.[8] Complexes of LPVP with richlocain were studied for comparison.

The compositions of LPVP–richlocain complexes were determined by an aviscometric method, and the ratios of components were expressed as both mass and the volume. With both methods of concentration expression, the bend on the plots of change of reduced viscosity of LPVP versus drug concentration is observed at the ratio *n* = [LPVP]:[richlocain] = 2:3. Using a crosslinked polymer carrier, the composition of the gel–drug complex was determined from plots of change of swelling coefficients K_S of gels versus richlocain solutions of different concentration.[7] As seen in Figure 1, the K_S values of the gel decrease due to binding and reach the smallest value at *n* = [GPVP]:[richlocain] = 1:1 (K_S = 12 g/g). With further addition of richlocain, K_S values increase. When a surplus of richlocain is reached, charges appear on the gel surface because richlocain is a positively charged mole-

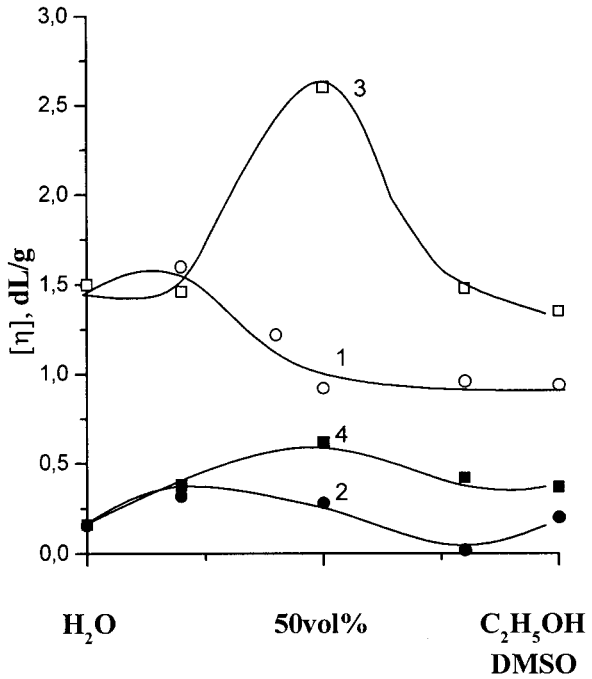

Figure 2 Dependence of intrinsic viscosity of linear PVP (1,3) and its complex with richlocain (2,4) on the composition of the water–ethanol (1,2) and water–DMSO (3,4) mixed solvents.

cule. All of the following investigations were carried out at this ratio of interacting components.

The observed decrease in the K_S of the initially swollen gel in the presence of the drug indicates an interaction between the polymer matrix and a low molecular weight substance. Polymer gels undergo volume–phase transitions due to changes of external conditions (pH, temperature, solvent nature, etc.) or due to interaction with complementary macromolecules and some low molecular weight substances (metal ions, drugs, surfactants, etc.).[10] The degree of binding, determined from the concentration of richlocain in the supernatant, is ~15%. It is known that ionic bonds are the most preferred for binding of drugs with polymers,[11] so this low degree of binding reflects the nonionic nature of the polymer matrix. The weak donor–acceptor interactions between carbonyl groups of PVP and nitrogen atoms of the drug molecules, which are confirmed by the appearance of a new band at 1540 cm^{-1} in the infrared (IR) spectra of PVP–drug complexes,[6] as well as the hydrophobic interactions are obviously responsible for binding of PVP with richlocain.

The behavior of polymer–drug complexes with linear and crosslinked PVP was first investigated in the presence various medium properties. The dependence of intrinsic viscosity of free LPVP and its complexes with richlocain on the composition of water–ethanol and water–DMSO mixed solvents are shown in Figure 2. LPVP–richlocain complexes in water have a compact structure that is confirmed by intrinsic viscosity values ([η] = 0.13 dL/g) that are much lower than those for free LPVP ([η] = 1.47 dL/g). It is seen from Figure 2 that [LPVP]:[drug] = 2:3 complexes are stable to the action of organic solvents; that is, the structure of the complex does not undergo any significant changes due to different mixed solvent composition (Figure 2, curves 2 and 4). At the same time, the viscosity of free PVP noticeably changes in mixed solvents (Figure 2, curves 1 and 3).

Similar results are obtained for crosslinked PVP and its complex with richlocain ([GPVP]:[drug] = 1:1) in water–ethanol mixtures (Figure 3). The value of K_S increases up to 20 vol % ethanol content in the mixture. This result correlates with the improvement in the thermodynamic quality of the solvent for the free gel (curve 1) and destruction of gel–drug complex (curve 2). Therefore, both systems behave similarly, undergoing the some contraction of gel volume with increase of ethanol content in the mixture.

Complexes of linear PVP with richlocain in the ratio [LPVP]:[drug] = 2:3 in water are stable in the pH range 2.0–12.0 and at temperatures between 20 and 70°C. The intrinsic viscosity of complexes with LPVP does not change appreciably and is lower ([η] = 0.13 dL/g) than that of the free polymer ([η] = 1.47 dL/g). At the same time, the structure of complexes of crosslinked PVP with richlocain ([GPVP]:[drug] = 1:1) depends on pH (Figure 4). Swelling coefficients of free PVP gel as a nonionic polymer do not change over the entire pH interval studied (Figure 4, curve 1). Complexes of richlocain with GPVP-1 and GPVP-2 show similar behavior; that is, both contract in the acidic region and swell in the alkali region. At pH = 8, each

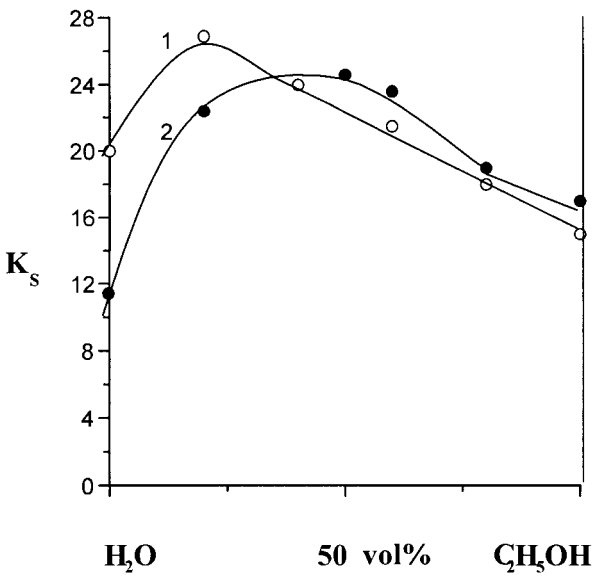

Figure 3 Dependence of swelling coefficients of GPVP hydrogel (1) and its complex with richlocain (2) on the composition of the water–ethanol solvent.

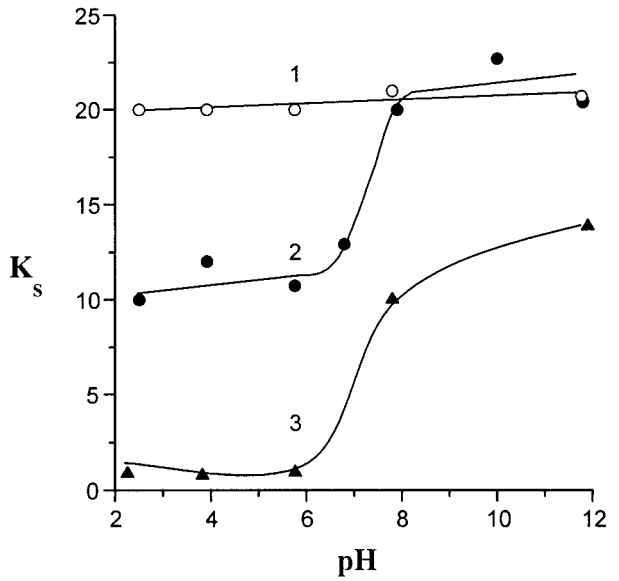

Figure 4 Dependence of swelling coefficients of GPVP-1 hydrogel (1), GPVP-1–richlocain (2), and GPVP-2– richlocain (3) complexes on pH.

complex has a K_S value equivalent to that of its respective free hydrogel (K_S = 20 for complex with GPVP-1 and K_S = 7 for complex GPVP-2). These results indicate that full destruction of gel–drug complexes occurs.

The kinetics of richlocain release from the [GPVP-1]:[drug] = 1:1 complex into water were studied, and the results are shown in Figure 5. At pH = 7.0,

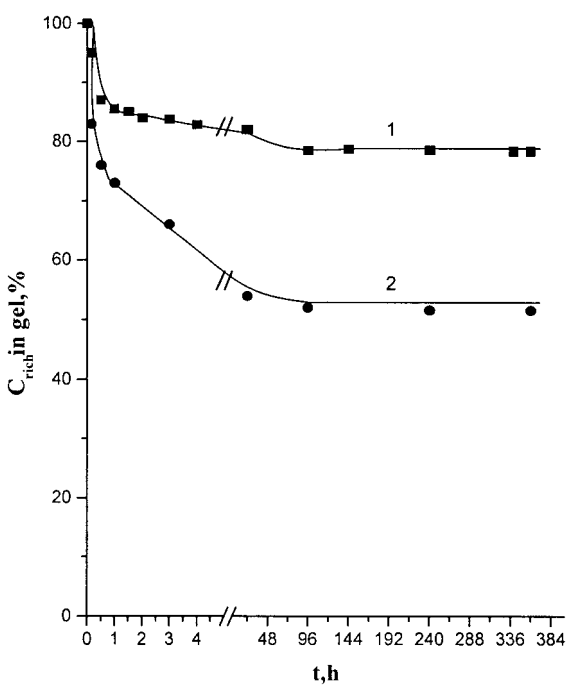

Figure 5 Kinetics of richlocain release from GPVP-1–richlocain complex: (1) pH = 7.0; (2) pH = 8.0.

TABLE I
Kinetic Data of Richlocain Desorption

System	T, K	Log K	E_a, kJ mol^{-1}
GPVP-1–richlocain	293	4.25	
	298	4.15	6.86
	310	0.80	
	323	0.40	

~20% of richlocain is released within 96 h. This quantity remains constant up to 384 h, indicating poor desorption of richlocain. Comparatively, complexes of richlocain with sodium polyacrylate and betain-type polyampholyte gels display better desorption; that is, the degree of release of richlocain reaches ~100% within 144 h and ~80% within 260 h, respectively.[7] The quantity of realized richlocain increases to ~50% at pH = 8.0 (Figure 5, curve 2), obviously indicating the destruction of the GPVP-1–drug complex at this pH.

To determine the activation energy of desorption of richlocain from the gel matrix, the kinetics of drug release at different temperatures were measured. The experimental data were plotted as log $(C_\infty - C_0)/(C_\infty - C_t) - t$ (where C_0 is the initial concentration of richlocain within gel matrix, C_t is the concentration of released drug at time t, C_∞ is the concentration of drug at $t \rightarrow \infty$, and t is time in hours).[12] The desorption constants log K were determined from these plots. The activation energy, E_a, was calculated from the linear dependence of log K on the inverse of temperature $(1/T) \times 10^3$ (Table I). This value is the same order of magnitude as those reported for sodium polyacrylate gel–richlocain (E_a = 5.26 kJ mol^{-1}) and betain-type polyampholyte gel–richlocain (E_a = 17.14 kJ mol^{-1}) complexes.[7] The larger value of E_a in the case of polyampholyte gel indicates the possible participation of both the acid and base groups of the polymer matrix in the binding.

CONCLUSIONS

The immobilization of an anesthetic drug richlocain into linear and crosslinked PVP was investigated. The immobilization is realized because of complex formation between polymer and drug. These complexes have a definite composition. The properties of polymer–drug complexes were investigated with respect to change of external factors, such as thermodynamic quality of the solvent, pH, and temperature. Linear PVP–richlocain complexes were stable in water–organic solvents mixtures and were unaffected by changes in pH in the range 2.0–12.0 interval and changes in temperature in the range 20–70°C. Complexes of PVP gel with richlocain are destroyed both in water–ethanol mixtures containing 20 vol % ethanol and at pH = 8.0 as indicated by the increase in the

swelling coefficients of these complexes to the values of free gel. The results of these kinetic investigations confirm the prolongation of drug release from a gel matrix.

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