Interaction of richlocain with some linear and crosslinked polymers

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Abstract

The interaction of local anesthetic drug richlocain with linear polyacrylic acid and crosslinked sodium polyacrylate, linear and crosslinked acrylic acid–Schiff base copolymers has been investigated. The compositions of forming polymer–drug complexes were determined. The influence of external factors such as pH, ionic strength, temperature and thermodynamic quality of solvent on the stability of these complexes was studied. The kinetics and activation energy of drug release from the gel matrix has been evaluated. © 2002 Published by Elsevier Science Ltd.

Keywords: Complexes; Collapse; Interaction

1. Introduction

Generally the field of medicine needs highly effective drugs deprived from secondary effects for application in anesthesiology. Richlocain is a new and effective local anesthetic drug registered in CIS countries and acts like novocain, lidocain, trimecain and cocain [1]. In medicine, richlocain is applied as only isotonic injection solution. Therefore, the development of prolonged dosage form of richlocain with the help of water soluble and water-swelling polymers to control the release rate of drug from the dosage forms is very prospective. According to Ref. [2] there are five mechanisms of controlled drug delivery: (1) diffusion, (2) dissolution, (3) osmosis, (4) ion-exchange, and (5) polymer prodrug. The present communication considers the electrostatic immobilization of positively charged drug richlocain into negatively charged polyelectrolyte and ion-exchange release mechanism of drug from the macro-molecular coils and gel matrix.

2. Experimental

2.1. Materials

Richlocain (**1**), the commercial product of Asfarma Ltd (Russia), was used without purification. Maximum absorption of (**1**) is observed at $\lambda = 275$ nm [3].

Linear polyacrylic acid (**2**) with weight average molecular weight $M_w = 450 \times 10^3$ was purchased from 'Polyscience' (USA) and used without purification.

Betaine type polyampholyte (AA–Sb) (**3**) was synthesized from Schiff base and acrylic acid by Michael addition reaction followed by radical copolymerization of purified distillation monomers in water–ethanol mixture in the presence of azobisisobutyrionitrile (AIBN) ($C = 5 \times 10^{-3}$ mol l^{-1}) as initiator. Polymer was purified by threefold precipitation from water–ethanol mixture into diethyl acetate. The copolymer composition determined by back titration is equal to [AA]/[Sb] = 48:52 mol%. The intrinsic viscosity [η] of polymer in 0.002 N HCl is equal to 26.0 dl g^{-1}. IR spectra of polymer sample confirm the presence of amine and carboxylic groups in polymer chains.

Crosslinked AA–Sb copolymer (**4**) as well as crosslinked sodium polyacrylate (**5**) were synthesized by radical polymerization in the presence of initiator AIBN ($C = 5 \times 10^{-3}$ mol l^{-1}) and crosslinked agent $-N,N-$methylene-bis-acrylamide (5×10^{-2} mol%). Aqueous solution of corresponding monomers were placed into a glass ampoule and bubbled by argon to remove the oxygen. The ampoule was then sealed and thermostated at 70 °C for some time. In order to remove the impurities the crosslinked sample was repeatedly washed with distilled water for 2–3 weeks and then dried in vacuum to constant weight at room temperature. The dried product was ground to powder. Composition of (**4**) accordance to back potentiometric

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titration of amine and carboxylic groups is equal to $[AA]/[Sb] = 65:35$ mol%. The swelling coefficients (K_s) determined gravimetrically as mass of water per 1 g of dried gel are equal to 155 g g^{-1} for (4) and 950 g g^{-1} for (5) in water.

The polymer–drug (2–1) and (3–1) complexes were obtained by mixing the aqueous solutions of interacting components.

The hydrogel–drug (4–1) and (5–1) complexes were obtained by adding definite concentration of aqueous solution of (1) to swollen gel. The gel–richlocain mixtures were equilibrated for 4 h. (4–1) and (5–1) complexes were separated from the solution, dried in vacuum and powdered for further investigations.
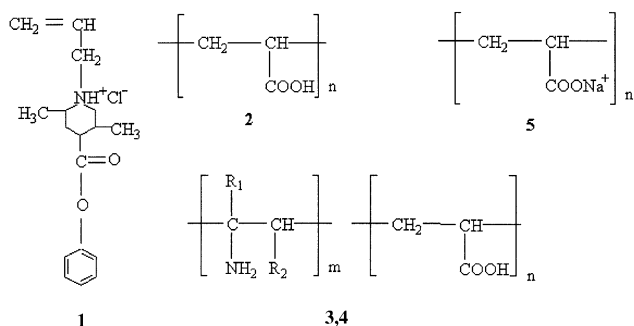
2.2. Instrumentation

Potentiometric and conductimetric titrations were carried out on the pH/conductivity meter 'Mettler Toledo MPC 227' (Sweden) at room temperature.

The concentration of immobilized into gel matrix (1) was determined with the help of spectrophotometer 'SF-16' (Russia) at $\lambda = 275$ nm by measurement of optical density of supernatant.

The swelling coefficients (K_s) of gels and gel–drug complexes were determined gravimetrically as mass of water per 1 g of dried gel.

The viscosity of the solutions was measured in an Ubbelode viscometer.

Reagent-grade solvents were used.

The ionic strength of the solution was adjusted to the indicated value with the neutral salt KCl.

IR spectra of (3) solid sample were recorded with the help of FTIR spectrometer (Nicolet).

3. Results and discussion

According to the principles of physico-chemical analysis [4], the deviation of the property of binary mixtures from the additive characteristic testifies about the formation of a new compound (polymer complex) with definite composition. Stoichiometry of polymer–drug complex found from the bend of conductimetric curve is equal to $[2]/[1] = 2:1$
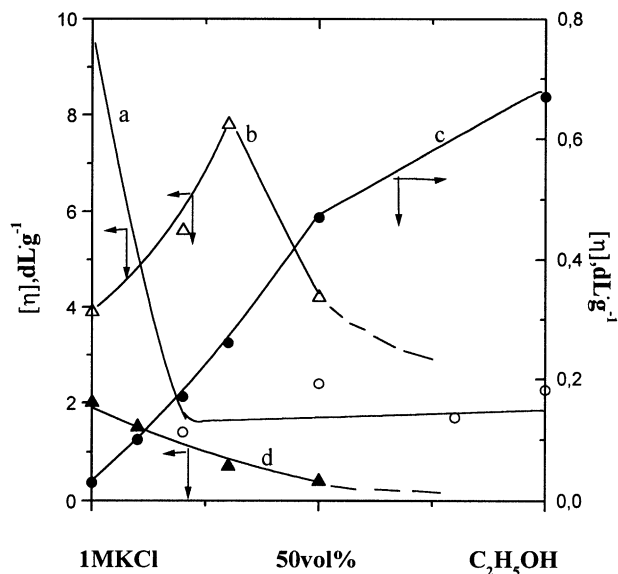

Fig. 1. Dependences of intrinsic viscosity (a) (2) and (b) (3) linear polymers, (c) (2–1) and (d) (3–1) polymer–drug complexes on composition of 1 M KCl–ethanol mixtures.

base mol l^{-1}. Complex (2–1) shows the polyelectrolyte behavior in pure water and the polyelectrolyte anomaly is fully suppressed at the ionic strength $\mu = 1$ M KCl. Due to poor solubility of (1) in water (maximum solubility of (1) in hot water is 1.5×10^{-2} mol l^{-1}) very diluted solutions were used.

The polyelectrolyte anomaly disappears in water–ethanol mixtures. As seen from Fig. 1 the complex particles gradually unfold upon addition of ethanol to 1 M KCl solution of (2–1) (Fig. 1c). The intrinsic viscosity of complex that is equal to $[\eta] = 0.03$ dl g^{-1} in 1 M KCl increase up to $[\eta] = 0.65$ dl g^{-1} in pure ethanol. This is explained by the improvement of solvent quality with respect to the hydrophobic parts of complex particles and weakening of the ionization state of macromolecules.

The intrinsic viscosity of pure (2) in dependence of solvent quality changes in contrast to (2–1) (Fig. 1a), the size of polymer chains decreases when ethanol content increases in 1 M KCl–ethanol mixture.

Since the interaction between (2) and (1) is electrostatic, one can expect considerable change in conformation of complex particles with the change in pH values. The dependence of reduced viscosity of pure (2) and (2–1) complex on pH is represented in Fig. 2. As seen the cooperative destruction of coiled structure of complex particles occurs in a narrow interval of pH change, η_{sp}/C sharply increases from 0.07 up to 0.95 dl g^{-1}. For (2–1) complex it is observed that the clearly expressed minimum at pH ~ 3.0 absent for (2), e.g. polymer–drug complex stabilized by ionic bonds shows amphoteric character that is inherent to polyelectrolyte complexes. Amphoteric behavior of polyelectrolyte complexes was demonstrated for copolymer acrylic acid and vinylbutyl ether/poly-N-methyl-4-vinylethynylpiperidinol-4 [5], sodium salt of polyacrylic
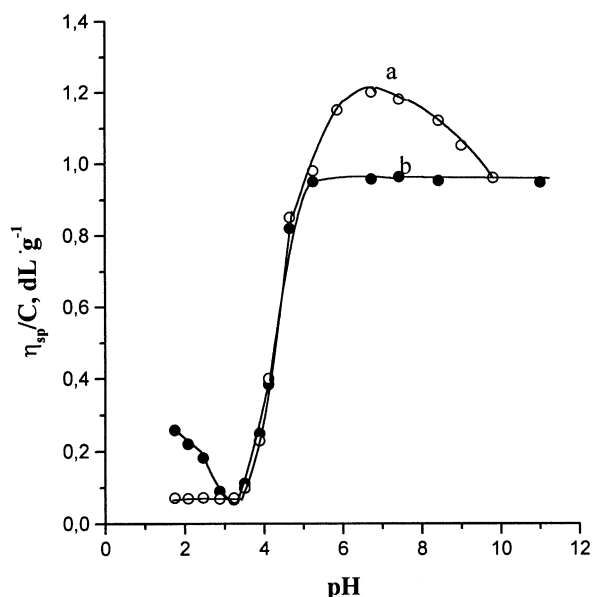
Fig. 2. Dependence of reduced viscosity of (a) (**2**−**1**) polymer−drug complex and (b) pure (**2**) on pH.

acid/poly[2(*N*,*N*-diethyl-*N*-methylaminoethyl)acrylate] [6], chitosan-polyacrylic acid [7] systems.

The composition of (**3**−**1**) polymer−drug complex is equal to [**3**]/[**1**] = 1:1 base mol l^{-1} according to curves of conductimetric titration. Solution of (**3**−**1**) complexes also discover the polyelectrolyte anomaly that is fully suppressed at the ionic strength $\mu = 1$ M KCl. The dependences of intrinsic viscosity of pure (**3**) and (**3**−**1**) complex on 1 M KCl−ethanol solvent composition are represented in Fig. 1b,d. For pure copolymer this dependence has extremum and the hydrodynamic size of polymer particles in 1 M KCl ([η] = 3.9 dl g^{-1}) is close to those in 1 M KCl− ethanol (50:50 vol%) mixture ([η] = 4.1 dl g^{-1}). Whereas (**3**−**1**) complex particles undergo the considerable
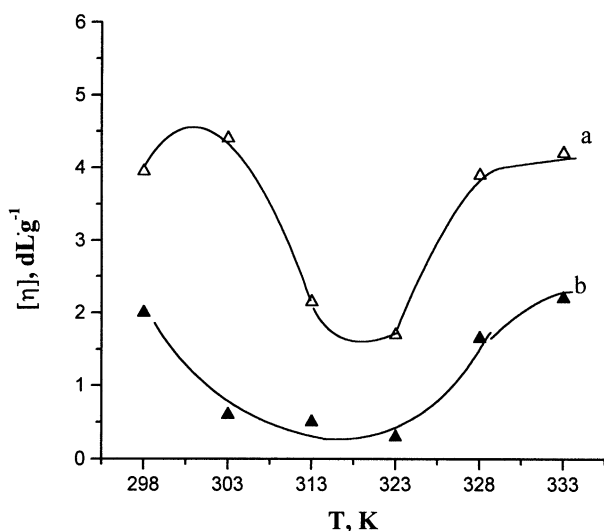

Fig. 3. Temperature dependences of intrinsic viscosity of (a) (**3**) and (b) (**3**−**1**) complex in 1 M KCl.
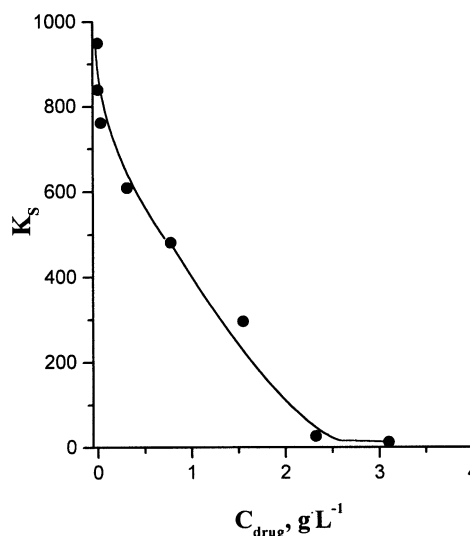

Fig. 4. Dependence of coefficients of swelling K_s of (**5**) on the concentration of richlocain. *C* of gel is equal to 0.2 g/l.

compactization ([η] changes from 2.0 dl g^{-1} to 0.04 dl g^{-1}, correspondingly). By increasing the ethanol content in mixture both pure (**3**) and (**3**−**1**) complex precipitates.

Both pure (**3**) and (**3**−**1**) complexes adopt the compact structure within 25–50 °C temperature interval (Fig. 3). However, the further increase in temperature up to 60 °C leads to unfolding of polymer particles.

The behavior of (**3**) and (**3**−**1**) complexes was also investigated in 1 M KCl−DMF mixtures. The solubility of polymer systems is observed only in mixtures containing ≤60 vol% DMF. At first the strong compactization of pure polymer and polymer−drug complex due to increase of hydrophobic interactions in polymer−solvent systems takes place. The compactization of (**3**) and (**3**−**1**) complex particles occurs at the content of DMF in mixture ∼30 and 50 vol%, respectively. The further increase in DMF content causes the unfolding of pure polymer and polymer− drug complex because the values of intrinsic viscosity increases.

Richlocain can also be immobilized into weakly crosslinked water-swelling polymers. These systems are very prospective for the development of new dosage forms [8,9]. We have investigated the interaction of (**1**) with sodium polyacrylate (**5**) and betaine type polyampholyte (**4**). Composition of (**4**−**1**) and (**5**−**1**) gel−drug complexes was determined from dependences of swelling coefficients K_s of corresponding gels placed into drug solutions of different concentrations [10]. As it is seen from Fig. 4 the swelling coefficient of initially swollen gel falls from $K_s = 950$ up to $K_s = 10$ g g^{-1} at the definite ratio of gel and drug solution and then does not change. Observed collapse of gel occurs due to the interaction of gel and drug containing the functional groups that are able to complex formation reactions. The composition of gel−drug complex

Table 1
Some characteristics of binding and release of richlocain

Gel	K_s of gel	Composition of [gel]/[drug] complex (mol mol^{-1})	K_s of gel–drug complex	Degree of binding (%)	Degree of release of drug (%)	Time of release (h)	Conditions
PAA–Na	950	1:10	10	~ 20	~ 100	144	Water, pH = 5.5
AA–Sb (65:35 mol%)	155	1:10	10	~ 50	~ 80	260	Water, pH = 5.5
					~ 80	50	Water, pH = 8.0

Table 2
Kinetic data of richlocain desorption at different temperatures

System	T (K)	$\log K$	E (kJ mol^{-1})
(5–1) Gel–drug complex	308	-0.22	5.26
	318	-0.04	
	328	0.1	
	348	0.34	
(4–1) Gel–drug complex	298	-0.74	17.14
	308	-0.48	
	318	0.08	
	323	0.23	

is equal to [gel]/[richlocain] = 1:10 mol mol^{-1}. Table 1 summarizes the data for both systems.

The kinetic curves of the drug release from gel matrix are shown in Fig. 5. There is a considerable release of the drug from the gel matrix for 24 h. The complete release of the drug reaches after 144 h. According to kinetic data the amount of drug released from the gel matrix is $\sim 100\%$. Analogous measurements were carried out for (4–1) gel–drug complex (Table 1). It was found that richlocain is released up to 80% for 50 h at pH = 8.0 and for 260 h at pH = 5.5 (pure water), e.g. the release of the drug into pure water is much more prolonged. This is probably connected by the fact that at pH = 8.0 (4–1) complex is already partially destroyed but it is far from the full destruction because K_s of (4–1) complex is equal to 40 g g^{-1} (pH = 8.0) while K_s of pure (4) is equal to 105 g g^{-1} (pH = 8.0) and to 155 g g^{-1} (pH = 5.5). In order to prolong
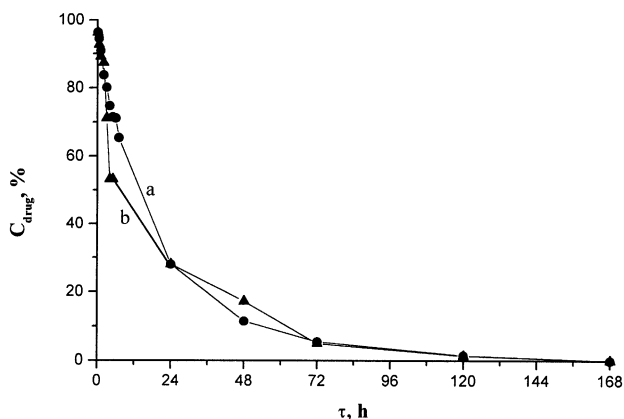
the drug delivery time probably it is necessary to keep the (4–1) gel–drug complex in fully collapsed state in water (pH = 5.5, $K_s = 10$ g g^{-1}).

The rate of desorption of (1) from the gel–drug complexes was measured in pure water (pH = 5.5) at different temperatures in order to evaluate the activation energy of drug release. The experimental data were plotted in coordinates $\log(C_\infty - C_0)/(C_\infty - C_t) - t$ (where C_0 is the initial concentration of (1) within gel matrix, C_t, the concentration of released drug at definite time t, C_∞, the concentration of drug at $t \to \infty$, and t, the time in hours) [11] from which the desorption constants $\log K$ are determined. From linear dependences of $\log K$ on reverse temperature $(1/T) \times 10^3$ the activation energy E_a were calculated (Table 2). The low values of activation energy for investigated gel–drug systems reflect the easy release of richlocain from the gel volume.

The behavior of (4), (5) gels and (4–1), (5–1) gel–drug complexes was investigated with respect to change of solvent quality and pH. Fig. 6 shows the swelling behavior of pure gels (4), (5) and (4–1), (5–1) gel–drug complexes in water–ethanol mixture. Sharp decrease in K_s for (5) with increasing ethanol content is observed. It is probably connected with poor thermodynamic quality of the solvent
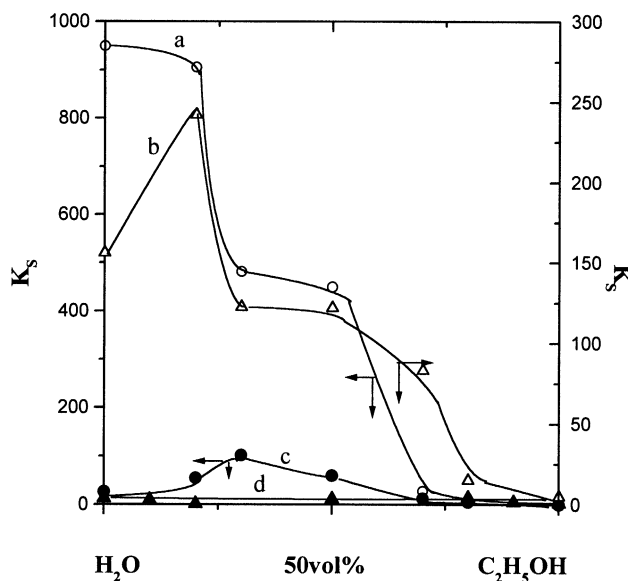

Fig. 5. Kinetic curves of release of (1) from (5–1) gel–drug complex: (a) pH = 5.5; (b) pH = 6.3.

Fig. 6. Swelling behavior of gels (a) (5) and (b) (4) and (c) (5–1) and (d) (4–1) gel–drug complexes in water–ethanol mixtures.

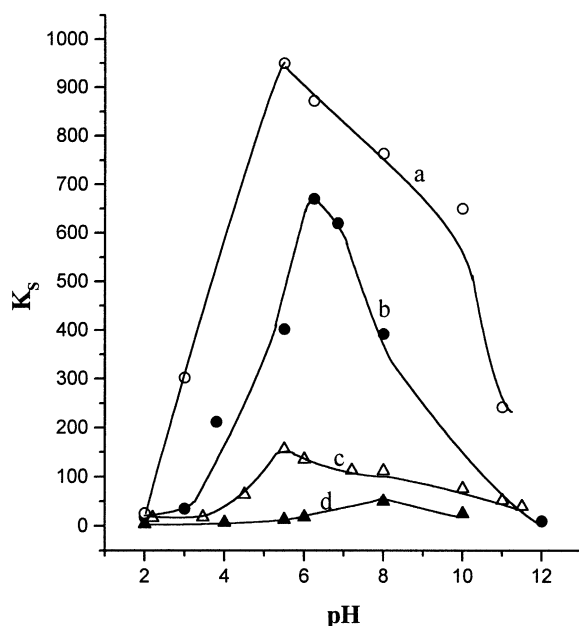Fig. 7. Dependences of K_s for (a) (**5**) and (b) (**5**−**1**), (c) (**4**) and (d) (**4**−**1**) systems on pH.

with respect to ionic groups of polyelectrolyte gel. At the same time (**5**−**1**) drug–gel complex (Fig. 6c) remains in collapsed state in water–ethanol mixture and reswells insignificantly in 60:40 vol% water–ethanol mixture. Swelling coefficient of (**5**−**1**) complex in this mixture reaches up to 100 g g^{-1} and deviates considerably from K_s of pure gel (**5**) ($K_s = 950$).

The behavior of polyampholyte gel (**4**) and its (**4**−**1**) complex with drug is similar. Pure (**4**) gel undergoes the collapse, swelling coefficients change from $K_s = 155$ in water to $K_s = 10$ in ethanol while (**4**−**1**) gel–drug complex stays in collapsed state in all interval of change solvent composition (Fig. 6b,d, respectively).

Fig. 7 shows the dependences of swelling coefficients K_s of pure (**4**), (**5**) gels and (**4**−**1**), (**5**−**1**) gel–drug complexes on pH. The initial (**5**) has pH = 5.89. In dependence of pH gel undergoes the contraction in basic and acidic regions (Fig. 7a), while (**5**−**1**) complex (initial pH = 2) gradually destroys at pH = 2.0–6.5 interval and swelling coefficients change from 10 up to 670 g g^{-1}. But further pH increase causes the shrinking of complex particles again (Fig. 7b).

For (**4**) and (**4**−**1**) polyampholyte–drug system, a similar behavior is observed (Fig. 7c,d, respectively).

4. Conclusion

Immobilization of richlocain into linear and crosslinked polyelectrolytes has been realized. The composition of linear polymer–drug and gel–drug complexes have been found. The properties of forming complexes were investigated with respect to change in external factors such as thermodynamic quality of the solvent, pH and temperature. The destruction conditions of gel–drug complexes have been found. The low values of activation energy for gel–drug systems reflect the prolongation of drug release from the gel volume.

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