

Sorption of Richlokain on Polycarboxylic Acid Gels

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Abstract

The sorption immobilization of richlokain on gels of polyacrylic acid (PAAG) or polymethacrylic acid (PMAAG) has been studied. By a number of methods – equilibrium swelling, potentiometry, IR-spectroscopy, and sorption it has been shown that binding of richlokain with these gels leads to the complex formation owing to the electrostatic interaction, which is stabilised by the hydrophobic and hydrogen bonds. Effect of an ionic force, reagent concentration, cross-link degree, hydrophobic nature of gels, and pH of solutions on the sorption process has been studied.

Introduction

Analysis of the literature sources shows that the polymer gels are perspective material for the production of prolonged form of medical products, and for the controlled transfer and extraction of acting agent. Polymer gels have a unique ability to respond to the slightest fluctuations of the conditions of medium by a change of hydrodynamic parameters [1-3]. Besides, they are easy to use: easy removal from the wound surface without injuries of the new growing tissue; there is no necessity to use the bandages and unpleasant procedure of injection; and they soak up pus and exudations *etc.* [3,4].

Basically two methods are used for immobilisation of medical products on the polymer gels: a) introduction of the polymer gels into an aqueous monomer solution with the following polymerisation; b) adsorption of the medical product on the gel prepared [1,5]. Each method has both advantages and disadvantages. For each concrete case it is necessary to select the most reasonable approach with taking into account the individual specifics of both polymer support and medical product.

Since the chemical and medical properties of both polyacrylic (PAAG) and polymethacrylic (PMAAG) gels were widely studied, they have an interest as the model systems.

Recently the properties of gels (PAAG and PMAAG) were investigated at introduction of richlokain by the first method [6,7]. Richlokain (RH) is a medi-

cal product having analgesic action. In this paper the sorption immobilisation of richlokain on PAAG or PMAAG, as well as the properties of the polymer derivatives of richlokain are presented.

Experimental

The gels of polyacrylic and polymethacrylic acids were produced by the radical co-polymerisation of acrylic and methacrylic acids, respectively with 10% solution of a cross-linking agent (CA) in ampoules with argon medium at 343 K and at presence of diazo-bis-isobutyric acid (DABIBA), which has been used as an initiator. Mass of DABIBA is 0.5% of monomer mass. Methylen-bis-acryl-amide (MBAA) has been used as a cross-linking agent. Duration of polymerisation was 1 hour. Gel produced was washed by distilled water to remove the non-reacted monomers. The completeness of washing has been tested by a qualitative reaction with bromine water.

The gel composition was determined by the elemental analysis and potentiometric titration.

The elemental analysis was provided by PERKIN ELMER Series/CHNS/0 Analyzer 2400 (USA). Results are presented in Table 1.

According to the data of Table 1 the differences between the theoretical and experimental values are not significant. Therefore the initial content of MBAA have been accepted without any additional correction. The sorption exchange capacity of gels has been determined by the direct titration of samples of swollen gel with an alkali solution at equilibrium state [8].

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Table 1
Results of elemental analysis

Gel	MBAA	Content of elements, %					
		C		H		N	
		calculated	experimental	calculated	experimental	calculated	experimental
PAAG	0.1	50.01	49.90	5.56	5.73	0.04	0.04
PAAG	0.25	50.02	49.95	5.56	5.78	0.10	0.09
PAAG	0.5	50.05	49.97	5.50	5.74	0.19	0.18
PMAAG	0.25	56.09	55.70	7.01	7.25	0.08	0.07
PMAAG	0.5	55.81	55.42	6.92	7.16	0.16	0.15

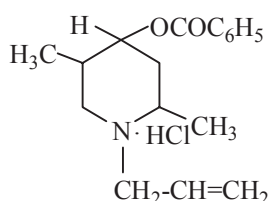
Physico-chemical characteristic of gels are presented in Table 2.

Table 2
Physico-chemical characteristic of gels

Content [CA], %	PAAG			PMAAG	
	0.1	0.25	0.5	0.25	0.5
ρ , g/cm ³	1.423	1.545	1.763	1.378	1.675
SVC, mg-eq/g	10.8	10.4	9.6	9.2	8
α , g/g	670	354	299	290	193

Where, ρ – solidity of gels;
SVC – sorption volume capacity;
 α – swelling degree of gels.

Hydrochloride of benzoic ether of α -isomer of 1-allyl-2.5-dimethyl piperidol-4 (richlokain)



has been synthesised at the faculty of organic chemistry and natural compounds of al-Farabi Kazakh National University [9]. The preparation made in "Aspharma LTD" company (Russia) has been used without additional purification.

Potentiometric titration of solutions was carried out by using ion meter (EV-74, Russia) with glass and chlorine-silver electrodes in thermostatic cell with accuracy of ± 0.05 pH units.

Swelling degree (ratio) was determined by the equilibrium swelling method and was calculated as a

ratio of masses of swollen and dry samples [10]:

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

where, m_0 – mass of dry sample, g; m – mass of swollen sample, g.

Degree of electrostatic binding (θ) between richlokain and gels was calculated according to equation [11]:

$$\theta \times C_0 = g_{NaOH}/V + [H^+] - [H^+]_{PA}$$

where: g_{NaOH} – amount of alkali added at titration, g-equivalent; V – volume of a reacting mix, L; $[H^+]$ – concentration of hydrogen ions in mix, mol/L; $[H^+]_{PA}$ – concentration of hydrogen ions produced by the functional groups of polyacids non-reacted, mol/L; C_0 – base-mole, calculated according to a value of SVC (sorption volume capacity).

The thermodynamic parameters were calculated from temperature dependence of constant of binding between richlokain and gels by Van-Goff equation [12]. Constant of binding have been determined according to data on sorption by Hyu-Klotz [13,14]:

$$1/r = r/n + 1/n KC$$

where, n – number of binding centres; C – concentration of non-bounded richlokain, mole/L; $r = C^*/P$, C^* and P – concentration of bounded richlokain and polymer, respectively, mole/L.

Dependence of $1/r = f(1/C)$ is a straight line with tangent of inclination K/n . Enthalpy has been calculated from temperature dependence $\ln K = f(1/T)$ according to formula: $\Delta H = -R[d \ln K / d(1/T)]$. Then, $\Delta G = -RT \ln K$, $\Delta S = (\Delta H - \Delta G)/T$ were calculated [12,15,16].

For study of a sorption, a loading of dry gel was added in a solution with the fixed concentration of medical products. To determine the richlokain con-

tent water fraction was analysed by spectrophotometer ("SF-26", Russia) at wavelength of 234 and 274 nm, which are characteristic for the carbonyl and allyl groups. UR spectra of polyacids and complex with RH were determined by using UR-spectrometer "Mattson" (USA).

Results and discussion

Nature of binding between richlokain and gels of polycarboxylic acids

Study of turgescency shows that the drastic compression of gel size is occurred at immersion of both PAAG and PMAAG in richlokain solution. Figure 1 shows that polymer collapse is occurred at richlokain concentration is 1×10^{-3} M and 3×10^{-3} M for PMAAG and PAAG respectively.

The significant decrease of gel volume and collapse of polymer network can occur in consequence of two reasons [17]:

- decrease of the osmotic pressure of gegentions in gel and their transfer to the external solution;
- the simultaneous accumulation of cations of the complex organic molecules bonded by the electrostatic forces with the functional groups of polymer network.

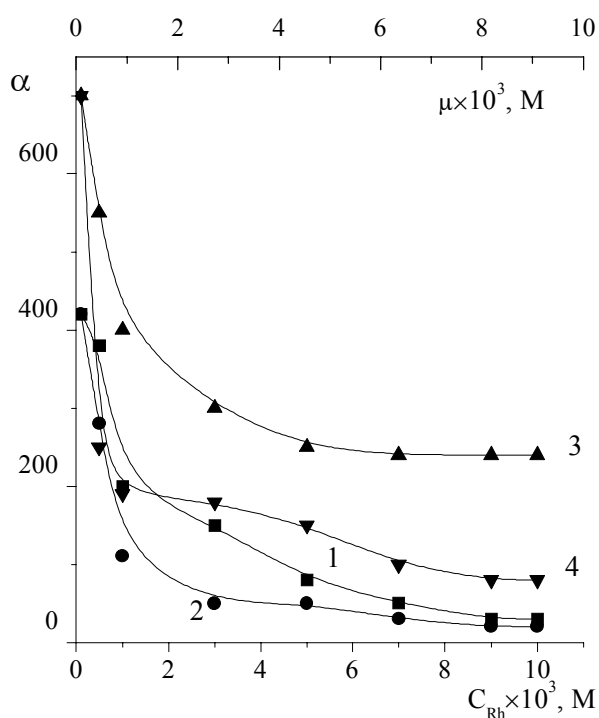


Fig. 1. Dependence of swelling degree of PAAG (1, 3); and PMAAG (2, 4) on richlokain concentration (1, 2) and ionic force (3, 4); $[CA] = 0.25$ mole %.

Depending on the conditions the network collapse can occur as a discrete or continuous conformational transfer, identifiable as a ball-globule transfer for the linear polymers [18,19].

On this basis it is possible to conclude that the drastic decrease of gel volumes is connected with the electrostatic binding of richlokain molecule with the polyacid carboxyl groups. In addition, liberation of H^+ cations into solution leads to compacting of the macromolecular ball. To elucidate the contribution of ionic force of richlokain ions in the gel compression, the effect of NaCl concentration, being a strong electrolyte, on the gel-swelling ratio has been studied (Fig. 1, curves 3, 4). It has been shown that though increasing of the ionic force leads to the significant decrease of network, nevertheless the swelling degrees of PAAG and PMAAG are higher than for equal richlokain concentration. In last case the solid salts of polyelectrolyte complexes of medical compound (MC) are formed. It indicates that the specific interactions play a main role in the complex formation between polyelectrolytes and richlokain. It causes the decrease of the network charge density at compression of polymer network.

Also, the ion exchange mechanism of the complex formation reaction is confirmed by the potentiometric titration. The data are presented in Fig. 2. At introduction of richlokain solution in the gel-containing system the pH is decreased to values of $n = [RH]/[base-mole PA] \approx 0.5$, where RH is richlokain and PA is polyacid. In range of $n > 0.5$ the formation of compact aggregates of the salt of PA-RH complexes of white colour and insoluble in water is occurred. It corresponds to the data on turgescency.

In IR-spectra of complexes synthesised the adsorption bands, being specific for PA and richlokain are observed. Thus, the specific band for valency vibrations of CH-bonds (704 cm^{-1}), C=C-bonds of benzene ring (1584 cm^{-1}) and C=C-bonds of allyl groups (1638 cm^{-1}) are presented in IR-spectra. The intensive band at 1416 cm^{-1} assigned to the carboxylate ions of carboxylic acids is presented too. And in addition, the vibrations of ester bond of benzene fragment at 1712 cm^{-1} and intensive valency vibrations of C-N-bond at 1496 cm^{-1} are observed.

The data of the potentiometric titration of free polyacid gels and their mixes with richlokain allow to determine the degree of electrostatic binding (θ) of medical compound (MC) with polyelectrolytes [11]. In general, θ is expressed as a ratio of the concentration of ionic bonds formed by groups of polymer

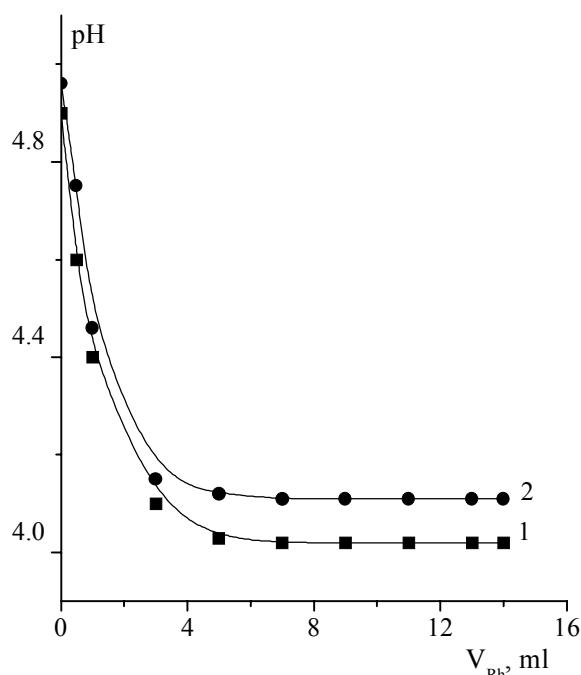


Fig. 2. Curves of potentiometric titration of PAAG (1) and PMAAG (2) $[RH] = 0.01$ M; $[CA] = 0.25$ mole %.

network and richlokain ions (C_K) to the total concentration of functional groups of PA network (C_0) calculated from a value of sorption volume capacity (SVC). Calculations show that the low θ values of 3–5% are reached at the reaction conditions. The significant increase of θ may be achieved by the growth of pH of a medium. At that the drastic θ increase at growing pH occurs in a narrow range. It indicates that the complex formation between richlokain and gels has the high cooperative character (Fig. 3) [20]. There are some reasons for that: 1) neutralisation of the low-molecular acid formed during the ion exchange reaction and shift of equilibrium towards complex formation; 2) strengthening of ionisation of PA carboxyl groups responsible for electrostatic binding and consequently strengthening of gel turgescency with increasing pH; it promotes the binding of richlokain with the macromolecular network.

Quantitative characteristics of sorption of richlokain on gels of polyacids

The results of the electrostatic binding demonstrate, that at interaction of richlokain with PAA and PMAA gels the small values of θ ($\leq 5\%$) are reached. It needs to note, that the modern theories on sorption of ions of the complex organic molecules by the network polyelectrolytes attach a great importance to

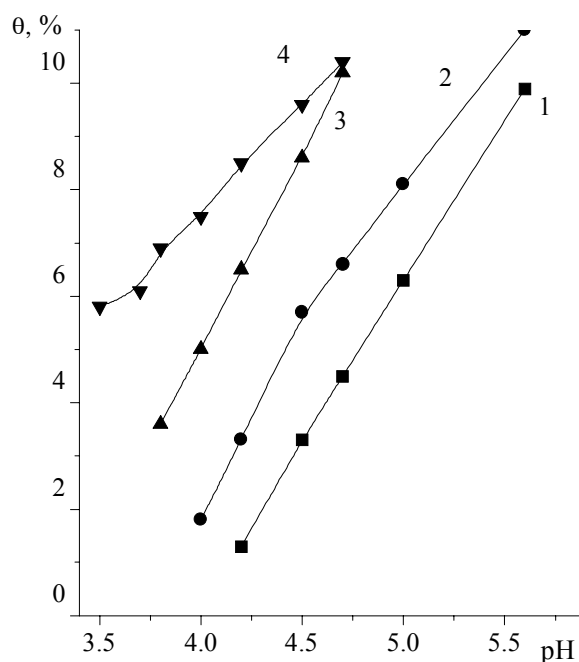


Fig. 3. Dependence of the degree of electrostatic binding of richlokain with PAAG on pH of medium at $n = 0.1$ (1); 0.3 (2); 0.5 (3) and 2 (4); $[CA] = 0.1$ mole %.

the Coulomb interactions and additional interactions, such as the hydrogen and hydrophobic ones [21]. Because of the PA gels and richlokain contain the functional groups and hydrocarbon radicals, which are able to carry out the hydrogen and hydrophobic interactions, it is possible to suppose that the total degree of richlokain binding with PA network should be much higher. These data may be obtained by the investigations of the quantitative characteristics of sorption of medical compound on the gels.

The kinetic curves of richlokain sorption on PAAG and PMAAG are presented in Fig. 4. It is shown, that the amount of medical compound sorbed is increased with increasing time. The maximum values are $\sim 30\text{--}60 \times 10^{-5}$ mol/g depending on the gel nature. Increasing the gel cross-link degree is accompanied by the decrease of richlokain sorption and increase of time required to get the maximum sorption values. Thus, if for PAAG with content of cross-agent is 0.1 mole % the maximum value of richlokain sorption is reached during 2–3 hours, then for gels containing 0.25 and 0.5 mole % of MBAA it needs 3 and more days. Probably, it is connected with the increase of the frequency of polymer network and decrease of penetration factor for diffusing molecules of the medical compound. The data presented in Figure 4 show, that in compare with PAAG the PMAAG is characterised by the lowest value of richlokain sorption. It may be caused by the high hydrophobic nature of

PMAAG, which is able to the inter-molecular hydrophobic interactions and to create the steric difficulties for the sorption of medical compound.

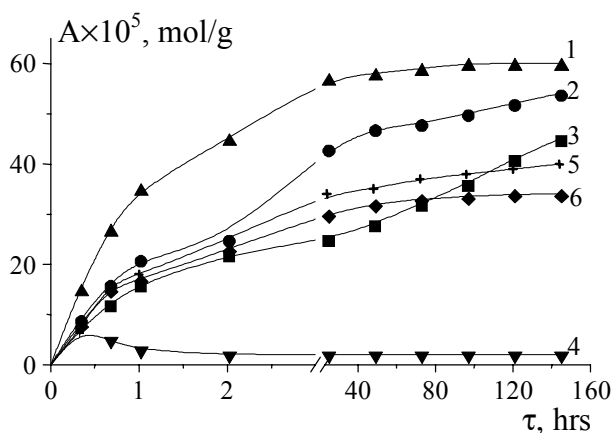


Fig. 4. Kinetics of richlokain sorption on PAAG (1-4) and PMAAG (5, 6) in aqueous (1-3, 5, 6) and physiological solution (4); $[RH] = 5 \times 10^{-4} \text{ M}$, $[CA] = 0.1$ (1, 4); 0.25 (2, 5) and 0.5 (3, 6) mole %.

The data on diffusion coefficient calculated from swelling and sorption values [22] and presented in Table 3 confirm that. Decrease of diffusion coefficient of richlokain is observed at increase of gel cross-linking. The diffusion coefficient is less for PMAAG than for PAAG, it clearly explains the differences between their sorption properties.

Table 3

Coefficients of richlokain diffusion at sorption on PAAG and PMAAG, $[RH] = 5 \times 10^{-4} \text{ M}$

$[CA]$, %	PAAG	PMAAG
0.1	1.452×10^{-8}	—
0.25	0.682×10^{-8}	0.037×10^{-8}
0.5	0.138×10^{-8}	0.009×10^{-8}

According to [17] the intensive sorption can be explained by the following reason. At introduction of the polyelectrolyte gel into the surplus solvent the low-molecular gegenions tend to leave gel and to move into the external solution due to the entropy reasons to realize the maximum freedom of transmission movement. However, in accord with [23] such process is not possible, because the dissociated gegenions cannot overpass a distance higher than the Debay length and due to that they cannot leave the gel volume-gel should remain the electro-neutral state [23]. Other situation is occurred at presence of solvent ions

(richlokain ions). In this case the ion exchange between richlokain and ionised carboxyl groups of polymer network resulting in to emission of H^+ protons into solution is carried out, *i.e.* transmission entropy profit is occurred. By entropy reasons the uniform distribution of H^+ cations over all system volume is more preferable, therefore their concentration in gel phase is decreased and concentration of richlokain is increased. Hence the reasons of decreasing richlokain sorption in the physiological solution are becoming clear (Fig. 4, curve 4): at introduction of NaCl a profit of transmission entropy is decreased, because the network turgescency is decreased. Deterioration of the thermodynamic solvent quality and dissociation of COOH-groups of PA are the results of the indirect influence of salt additives [24].

According to the calculations, 15-17% and 12-15% richlokain are immobilised on PAAG and PMAAG, respectively. The low values of the linked medical compound and the long duration of establishment of equilibrium sorption values (≥ 3 days) indicate, that the interaction between gels and richlokain occurs on the "relay-race" mechanism. The diffusion of medical compound occurs through polymer network surface [19,25], *i.e.* it submits to so-called gel kinetics rules. According to [26,27] the inter-diffusion limitations take place at sorption on gels. That is characterized by the presence of linear parts at the beginning of kinetic curves and getting the equilibrium level of sorption during 5-10 days. It proves, that the diffusion transfer of molecules linked with the sorbent surface into gel volume is occurred, *i.e.* from periphery towards the gel center.

These opinions are confirmed by the kinetic data obtained at richlokain sorption on the preliminary swollen gels (Fig. 5). Figure 5 shows, that the character and quantity of richlokain sorption on swollen PAAG are similar to sorption on dry gels. Thus, the equilibrium values of richlokain sorption on the swollen PAAG depending on the degree of cross-linkage are $32-42 \times 10^{-5} \text{ mol/g}$ or 12-17%. These values are getting at MBAA content of 0.1 mole % for 2-3 hours and at 0.25 mole % for 2 days. It can be explained by the formation of the PAAG-MC complexes over the gel surface with the following transfer of richlokain molecules according to the inter-diffusion mechanism. Richlokain sorption on preliminary swollen gels is accompanied by the drastic contraction of gels, which is increased with a growth of the MC concentration as a result of polymer network compression (Fig. 6).

At Figure 7 the concentration dependences of

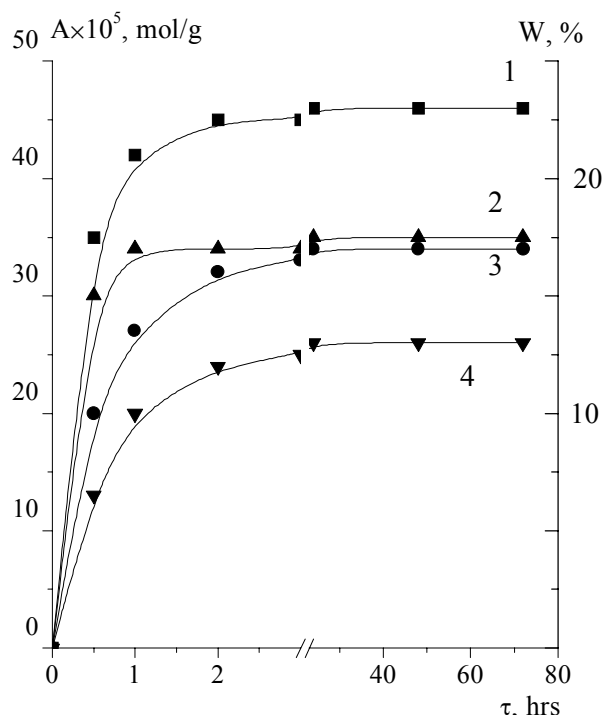


Fig. 5. Kinetics of richlokain sorption on swollen PAAG (mol/g) (1, 2) and (%) (3, 4). $[RH] = 5 \times 10^{-4}$ M; $[CA] = 0.1$ (1, 3); 0.25 (2, 4) mole %.

richlokain sorption on PAA and PMAA gels are presented. It is shown, that richlokain sorption is decreased with increasing cross-linking agent owing to the deterioration of permeability into gel phase. The sorption degree is linearly increased with growth of the MC concentration to 5×10^{-3} M, then at high values of concentration no significant changes are observed. According to the data of swelling in this range of concentration ($\geq 5 \times 10^{-3}$ M) the contraction of the polymer network is occurred as a result of decreasing a charge density and effect of ionic force. Obviously, that with increasing the medical compound concentration its binding degree in percentage expression is decreased, because presence of only a small part of richlokain in solution is required to get the equilibrium of complex formation.

Ratio of binding forces between richlokain and polyacid gels

From comparison of the isotherms of electrostatic and common binding of richlokain with polyelectrolytes gels (Fig. 8) calculated on a base of data of potentiometry and sorption it is clear, that the degree of common richlokain binding is much higher than the electrostatic one. While the degree of electrostatic binding of richlokain with gels is not exceed

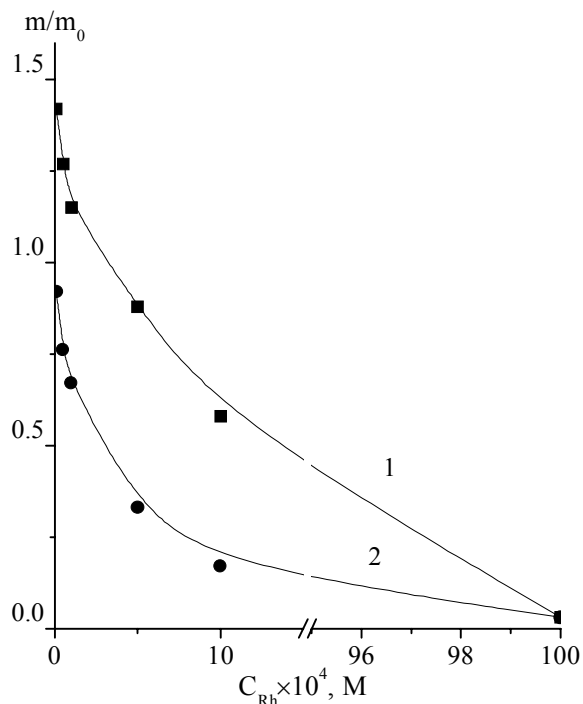


Fig. 6. Concentration dependence of swelling ratio of swollen PAAG (1) and PMAAG (2); $[CA] = 0.1$ (1) and 0.25 (2) mole %.

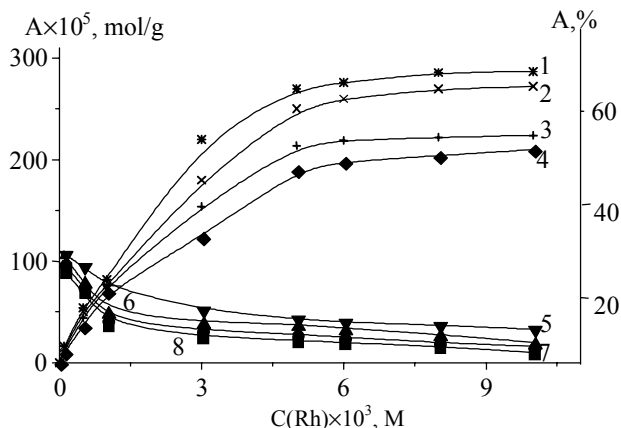


Fig. 7. Concentration dependence of richlokain sorption on PAAG (1-3, 5-7) and PMAAG (4, 8) by mol/g (1-4) and by % (5-8); $[CA] = 0.1$ (1, 5), 0.25 (2, 6), 0.5 (3, 4, 7, 8) mole %.

5%, the degree of common binding gets is 23-28% depending on the cross-linked degree and gel nature. It testifies to the dominating role of the additional interactions at binding of MC. It is obviously, that the ratio of electrostatic and non-coulomb forces at complex formation may be regulated by varying the external conditions: pH, ionic force, polymer nature, temperature *etc.* Also, the isotherms of binding show, that the maximum degree of electrostatic binding of richlokain is reached at relatively low molar ratio of richlokain and gels: $n \approx 0.5 \div 1.0$ in compare with the

common binding. In last case maximum degree is reached in field of $n \approx 3$. It can be explained, if to take into account, that firstly the ionic bonds are formed due to energy reasons, and then the hydrocarbon bonds with non-ionized carboxyl groups of polyacid and hydrophobic interactions of non-polar hydrocarbon radicals are formed.

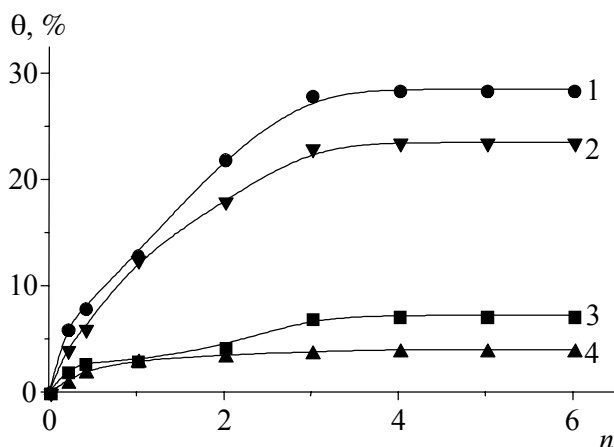


Fig. 8. Isotherms of total (1, 2) and electrostatic binding (3, 4) of richlokain with PAAG (1, 3) and PMAAG (2, 4); $[CA]=0.5$ mole %.

It is known, that the electrostatic interaction of polymers with low-molecular organic ions is accompanied by the heat production [28]. On other hand, the hydrophobic interactions of hydrocarbon radicals are strengthened with temperature growth, *i.e.* they have the endothermic character [28-31]. The hydrogen bonds are destroyed at increasing temperature. The total heating effect of the complex formation is determined by a ratio of heating effects of the electrostatic and non-electrostatic interactions. Consequently, the knowledge about the thermodynamic parameters of the complex formation can give the additional information about the process nature.

In Table 4 the thermodynamic parameters of richlokain binding with PAAG and PMAAG calculated on a base of the data on sorption of MC by gels at varying temperatures are presented [12-16]. It is shown, that interaction between richlokain with gels is characterised by the non-significant negative values of the free energy and positive enthalpy, by other words – by the endothermic characteristics. These data indicate, that the energies of hydrophobic interaction are dominated in compare with the electrostatic and hydrogen bonds at the process of complex formation. The enthalpy value is higher for more hydrophobic PMAAG (33.3 kJ/mol) in compare with

PAAG (20.8 kJ/mol), and it is an additional evidence of that. It is necessary to note a good correlation between the thermodynamic parameters of complex formation and data of isotherms of the electrostatic and total binding of richlokain with gels (Fig. 8).

Table 4

Thermodynamic parameters of binding of richlokain with PAAG and PMAAG, $[CA]=0.5$ mol %.

Gel	T, K	$-\Delta G$, kJ/mol	ΔS , kJ/mol	ΔH , kJ/mol
PAAG	280	6.972	0.078	20.785
	290	7.691	0.075	
	300	8.395	0.097	
PMAAG	280	13.092	0.166	33.256
	290	15.059	0.167	
	300	15.578	0.163	

Where, ΔG – change of Gibbs free energy,
 ΔS – change of entropy,
 ΔH – change of enthalpy.

Conclusions

Thus, the rules for binding of medical compound having the local anaesthetic act with the PA gels have been established. The results shows that the process of binding of richlokain with PA runs with the formation of the PA-richlokain complexes due to the ion exchange reaction, additional hydrophobic interactions and hydrogen bonds. The rate and sorption degree over the gels studied depend on a content of cross-linking agent, hydrophobic nature and MC concentration. The results of study may be used for the production of the prolonged gel forms of medical compounds by sorption method. For estimation of the prolongation effect it is necessary the data on the stability of PA-medical compound complexes and the rate of liberation of active initial compound from the polymer matrix. It is a subject for the further study.

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