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Novel mucoadhesive carriers based on alginate-acrylamide hydrogels for drug delivery

Marina Yu. Gorshkova,* Ludmila V. Vanchugova, Irina F. Volkova, Irina V. Obydennova, Ivan L. Valuev and Lev I. Valuev

A. V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, 119991 Moscow, Russian Federation. E-mail: mgor@ips.ac.ru

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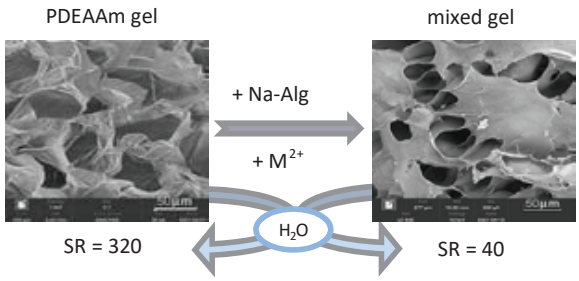
New mucoadhesive two-component carriers for drug delivery based on synthetic acrylamide/diethylacrylamide and natural alginate hydrogels have been synthesized. The introduction of sodium alginate into polyacrylamide/poly(diethylacrylamide) gels, followed by their crosslinking with metal ions, significantly changed structure and properties of hydrogels, such as swelling degree, drug capacity and drug release rate in physiological solution. The structure of the gels was characterized by FTIR spectroscopy and scanning electron microscopy.



Keywords: two-component hydrogel, interpenetrating networks, polyacrylamide, poly(*N*,*N*-diethylacrylamide), sodium alginate, covalent network, ionic network, drug delivery system.

Designing of new drug delivery systems aiming to enhance drug efficacy, its tolerance and safety of use is the rapidly developing direction in the biomedical polymer chemistry. Such means have already been used in various fields of medicine including cardiology, endocrinology, oncology, ophthalmology, *etc*. Hydrogels – networks of natural or synthetic polymers swollen in water – represent one of the most common types of carriers in drug delivery systems. Hydrogels are used in such systems for oral, parenteral (injection, implantation), transdermal, intrapulmonary or nasal administration.[1–10] We have previously studied the possibility of obtaining mucoadhesive formulations based on weakly cross-linked polyacrylamide gels for drug delivery to brain cells by means of nasal administration.[11] Mucoadhesion is a particular case of bioadhesion between two materials, at least one of them being a mucosal surface. The structure of gels ensures the retention of a drug for the requisite time directly at the required site on a mucous membrane and controlled release of a drug with desirable rate. The kinetics of drug release was largely determined by its nature and in the case of hydrophilic drug phenylalanine little depended on the composition of the gel, reaching 70–100% of administered amount in 10 min. At the same time, the release rate of this drug from alginate gels was determined by their cross-linking density.[12] Alginate was successfully used in preparation of various drug delivery systems including liposomes, microcapsules and other nanoparticles stabilized with alginate.[13–15] Modification of polyacrylamide hydrogels with alginate seems to be a promising approach for creation of new two-component carriers based on interpenetrating networks with high mucoadhesion and capable of providing desirable drug release rate. In these systems ionic networks formed by the interaction of charged groups of alginate with polyvalent ions will combine with covalent networks formed during polymerization. This approach allows the creation of so-called 'smart systems' based on the feedback operation principle hereby being able to change their properties under the influence of external factors, in particular temperature and ionic strength of the medium.

The purpose of this work was to synthesize new two-component hydrogels based on covalently crosslinked polyacrylamide (PAAm) or poly(*N*,*N*-diethylacrylamide) (PDEAAm) networks (structures of monomer units are presented in Online Supplementary Materials), obtained in the presence of sodium alginate (Na-Alg), followed by the formation of ionic network and to study the possibility of its use as a drug carrier. Lidocaine (LDC), a local anesthetic also known for its anti-inflammatory activity, has been chosen as a model drug. It has been proposed recently that LDC can be helpful in additional treatment of COVID-19.[16,17]

Materials based on mixed PAAm and Na-Alg gels are intended for use as membranes,[18] also synthetic cartilage and tendons have been described previously.[19–21] Such materials were synthesized at high concentrations of acrylamide and crosslinking agent using UV initiation or microwave irradiation. There are only a few publications concerning mixed gels of PDEAAm, most data relating to systems with PAAm,[22] polyvinyl alcohol,[23] chitosan[24] or graft copolymer ϰ-carrageenan-g-poly(methacrylic acid).[25] To our knowledge, there are no data concerning mixed gels based on Na-Alg and PDEAAm.

Herein, the PAAm/PDEAAm components of mixed gels were synthesized at concentration of monomers ⩽ 10 wt% that provide preparation of weakly crosslinked gels.[11,†] Figure 1

† Two-component hydrogels were prepared by radical copolymerization of AAm (w_{AAm} = 4.5 or 10% in reaction mixtures) or DEAAm (w_{DEAAm} = 4.5%) with crosslinking agent MBA (w_{MBA} = 0.06 or 0.6% to mass of monomer) under conditions of redox initiation [*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED) and ammonium persulfate (APS)

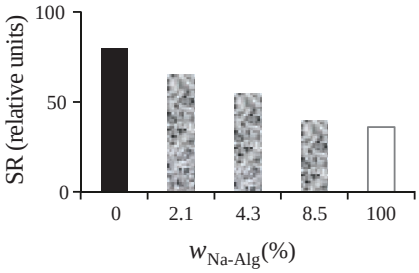


Figure 1 Swelling ratio (SR) dependence on Na-Alg content in the mixed PAAm hydrogels in water. Gel was prepared under condition: mass fraction of Na-Alg in total amount AAm and Na-Alg component in reaction mixture; mass fraction of AAm w_{AAm} = 10%, mass fraction of methylene-bisacrylamide w_{MBA} = 0.062% relative to AAm; Na-Alg : Fe^{2+} = 1 : 2.5 (molar ratio).

shows the values of swelling degrees of the PAAm hydrogels‡ obtained with different Na-Alg content. Concentration of Na-Alg was selected so that, on the one hand, the polysaccharide does not interfere with the formation of covalent network, therefore, a maximum mass fraction of Na-Alg does not exceed 1/20 of a total amount of monomer and Na-Alg, and on the other hand, it would allow us to trace the effect of Na-Alg addition. The introduction of Na-Alg into the reaction mixture caused the strengthening of weakly cross-linked PAAm hydrogels. For instance, the swelling degree of mixed gels containing 8.5 wt% of Na-Alg was halved compared to the swelling degree of one-component PAAm hydrogel. A similar dependence, but to less extent, was observed for PAAm hydrogels obtained at higher concentration of crosslinking agent (Table 1). The maximum decrease in the swelling degree of the mixed gels did not exceed 30% compared to one-component gels.

Apart from monomer and crosslinking agent concentration that controlled cross-link density, the swelling degree of the mixed gels is affected by chemical nature of synthetic polymer. Therefore, the presence of two ethyl groups in DEAAm monomer unit significantly increases the sensitivity of the gel to addition of polysaccharide. Thus, the addition of 16.5 wt% of Na-Alg into PAAm hydrogel resulted in an almost threefold decrease in swelling degree, whereas addition of the same quantities of Na-Alg into PDEAAm gel caused more than fivefold reduction of swelling degree. The similar behavior, but less pronounced, was observed for gels based on DEAAm and graft copolymer ϰ-carrageenan-g-poly(methacrylic acid).[25]

The properties of alginate hydrogels are known to be largely determined by the amount of the crosslinking metal (M) and its valency.[26] It is also proved for mixed hydrogels as shown in Table 1. The swelling degree of mixed hydrogels obtained in the presence of Fe^{2+} or Ca^{2+} differed slightly and were 50 and 38, respectively. At the same time, an increase in the metal ions amount results in significant rise in the crosslink density of alginate and therefore the swelling degree of the mixed hydrogels

w of each both is 0.1% to monomer amount] in the Na-Alg solution ($w_{Na\text{-}Alg}$ = 8.8 or 16.5% to total amount monomer and Na-Alg combined). The system was degassed to remove oxygen before polymerization. Aqueous solutions of $FeSO_4$ or $CaCl_2$ (Na-Alg : M^{2+} molar ratios of 3.8:1; 1:1; 1:3) were added in 2 h after the start of polymerization. After 1 h of stirring, the system was kept at room temperature for 24 h. Gels based on AAm and DEAAm were prepared in a similar way, but without introducing a solution of Na-Alg and metal salts. The alginate gels were obtained by adding aqueous solutions of $FeSO_4$ or $CaCl_2$ to Na-Alg solution with stirring and keeping the mixture at room temperature for 24 h.

‡ The swelling degree (swelling ratio) of the gels was determined by the formula SR = $(m_t - m_0)/m_0$, where m_0 and m_t are the masses of dry and equilibrium swollen gels, respectively.

Table 1 Dependence of the swelling degrees of hydrogels in water on the Na-Alg : M^{2+} molar ratio and the mass fraction of Na-Alg ($w_{Na\text{-}Alg}$) relative to total amount of monomers and Na-Alg. Conditions of preparing gels: w_{AAm} or w_{DEAAm} = 4.5%; w_{MBA} = 0.6% relative to amount of AAm or DEAAm.

Monomer	$w_{Na\text{-}Alg}$ (%)	Na-Alg : M^{2+} molar ratio	Swelling degree (relative units)
DEAAm	8.8	3.7 : 1 (Ca)	238
		1 : 1 (Ca)	68
		1 : 3 (Ca)	61
DEAAm	16.5	3.7 : 1 (Ca)	106
		1 : 1 (Ca)	39
		1 : 3 (Ca)	38
DEAAm	16.5	1 : 3 (Fe)	50
AAm	16.7	1 : 3 (Fe)	54
DEAAm	0	–	320
AAm	0	–	190

decreased. As expected, the metal content increase above the equimolar ratio with respect to carboxyl groups of polysaccharide did not affect the crosslinking density of the gel, regardless of the Na-Alg content.

The structure of mixed hydrogels was studied by FTIR spectroscopy. Spectral data (see Online Supplementary Materials) confirmed the presence of both acrylamide and alginate components in the mixed gels (characteristic bands of the both components are presented in the spectra). The shift of the bands of the carboxylate and amino groups relatively to the position in the spectra of one-component gels is particularly clear from difference spectra (see Figures S3, S5) and indicated the occurrence of additional interactions between polymer chains in mixed hydrogels most probably due to hydrogen bonds.[27–29] Evidently, the origin of the modifying effect of Na-Alg on the structure of PAAm and PDEAAm hydrogels is the additional interactions between the natural and synthetic polymer chains in the mixed hydrogels. Scanning electron microscopy (for details, see Online Supplementary Materials) confirmed this modifying effect (Figure 2). The initial hydrogels were characterized by rather fine structure. The introduction of Na-Alg into gels led to rearrangement of their structure, the pore size changed and their number decreased, which is in good agreement with the data on the swelling of gels.

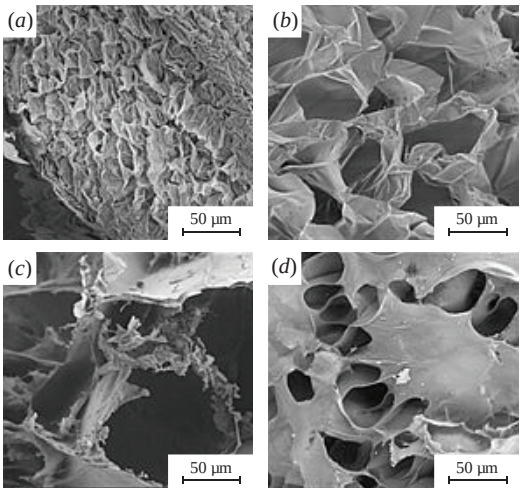


Figure 2 SEM images of the gels: (*a*) PAAm, (*b*) PDEAAm, (*c*) PAAm/Na-Alg, and (*d*) PDEAAm/Na-Alg.

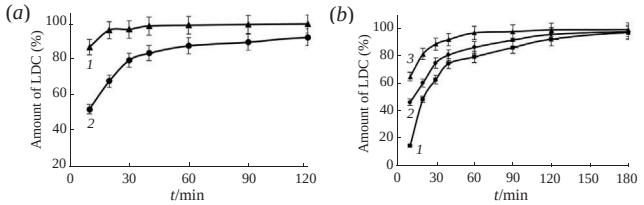


Figure 3 Kinetics of LDC release from synthetic gels and mixed gels based on (*a*) AAm: *1* - PAAm gel, *2*- mixed gel; (*b*) DEAAm: *1* – PDEAAm, *2–3* – mixed gels with different Na-Alg : Ca^{2+} molar ratio of (*2*) 3.8 : 1, (*3*) 1 : 1. PBS, pH 7.4.

Structural modification of PAAm or PDEAAm hydrogels with Na-Alg affects their LDC capacity and release profile.[§] Figure 3 shows kinetics of the release of LDC from hydrogels under conditions simulating physiological one: phosphate buffered saline (PBS), pH 7.4.

According to data of Figure 3, the ionic network in mixed gels effected differently on LDC release profile of PAAm and PDEAAm gels. The introduction of Na-Alg into gels based on PAAm slowed down the rather rapid release of LDC. The observed decrease in the drug release rate correlated with swelling degree of gels, so that the lower the swelling degree, the slower the release of drug. Thus, the release rate was limited by diffusion of the drug from gel pores. The addition of Na-Alg effected oppositely in the case of the gels based on DEAAm and increased the drug release rate. Besides, it is controlled by the cross-linking density of the polysaccharide. The amount of released drug depended on its content in the gel, that corresponds to its swelling degree (Table 2).

Thus, the results demonstrated that the introduction of Na-Alg into acrylamide gels followed by its crosslinking with metal ions leads to a significant change in their structure and properties, which makes it possible to regulate drug capacity and drug release rate of hydrogels. These results demonstrate the increased possibilities of biochemistry and polymer science in terms of the synthesis of hydrogels based on natural and synthetic polymers capable of changing their structure and releasing drugs in the desired way. Such systems would be useful for highly active, rapidly metabolizing drugs intended for the long-term treatment of chronic patients.

Table 2 Influence of the structure of the gels on the inclusion of LDC and the swelling degree of the gels in solution containing 5 wt% LDC and 0.33 wt% $CaCl_2$.

Gel	Na-Alg : M^{2+} molar ratio	LDC content in 1 mg dry gel/mg	Swelling degree
PDEAAm	0	1.1	22
PDEAAm mixed gels	3 : 1 (Ca^{2+})	1.7	33
	1 : 1 (Ca^{2+})	1.6	30
PAAm	0	2.6	54
PAAm mixed gel	1 : 3 (Fe^{2+})	1.5	30

[§] For the introduction of LDC into gels, freeze-dried samples were kept in 5 wt% LDC aqueous solutions containing 0.33 wt% $CaCl_2$ for 24 h. The prepared gels were used to study the kinetics of drug release under physiological conditions (PBS with 0.9 wt% sodium chloride and pH 7.4). The LDC concentration was determined by UV spectroscopy on a Specord M-40 instrument from the difference in optical densities of samples taken in experiments with LDC-containing gels and experiments with gels without drug. The concentration was calculated from the calibration dependences of the optical density at a wavelength of 271.4 nm on the LDC concentration. The results were presented as a dependence of the value of released amount of LDC calculated by the formula $(L_t / L_0) \times 100\%$ on time, where L_t is the current amount of LDC in the solution (mg), L_0 is the initial amount of LDC (mg) in hydrogel.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.03.012.

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