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Thermosensitive and mucoadhesive hydrogels based on modified alginate as drug carriers

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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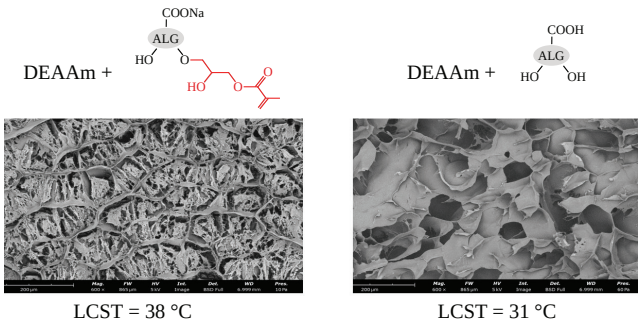
New thermosensitive mucoadhesive hydrogels based on a sodium alginate unsaturated derivative have been synthesized by copolymerization with *N*,*N*-diethylacrylamide (DEAAm) in the presence of a crosslinking agent. The formation of covalent bonds between the co-monomers has been shown to cause a significant change in the hydrogel supramolecular structure and makes it possible to regulate the lower critical solution temperature (LCST) of the gels. The possibility of using the hydrogels as drug carriers with a temperature-controlled drug release rate has been demonstrated in experiments *in vitro*.



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

Polymeric hydrogels, networks of natural or synthetic polymers swollen in water, are widely used in biomedicine.[1–7] Nowadays, there is a special attention to multicomponent hydrogels based on polymers of different nature whose networks are formed by different types of bonds, covalent, ionic, hydrogen binding, hydrophobic interactions or a combination two or more abovementioned interactions.[8–12] This approach is very promising because it makes it possible to improve the hydrogel properties significantly by combining the component features in one carrier. Besides, crosslinking the hydrogel components with different types of bonds can impart additional sensitivity to external effects. Thus, a rational choice of gel components and a network type can provide designing systems with a desirable set of properties such as biocompatibility, gel sensitivity to external influences, adjustable gel stability, required drug loading capacity, and release rate of a drug from a polymer matrix.

Recently, we have prepared mucoadhesive hydrogels based on covalently crosslinked polyacrylamide[13] and hydrogels of sodium alginate (SA) crosslinked with divalent metal cations.[14] Those hydrogels provided intranasal drug administration with retention at the injection site and delivery of the drug directly to brain cells. Besides, two-component mixed hydrogels have been developed and studied, with covalent networks being formed during acrylamide or *N*,*N*-diethylacrylamide (DEAAm) polymerization in the presence of a crosslinking agent in an SA aqueous solution and followed by ionic binding of SA carboxy groups by divalent calcium cations.[15] This allows controlling the hydrogel structure to provide the required loading capability toward the drug and its release rate into the physiological solution. Imparting thermal sensitivity, *i.e.* the temperature dependence of the hydrogel structure and properties, to hydrogel carriers expands the opportunities for controllable changes in hydrogel properties. Temperature sensitive synthetic polymers are commonly used for this purpose, *N*-alkyl-substituted polyacrylamides being one of them.[16] The synthesis of thermosensitive polysaccharide hydrogels involves either using synthetic polymers with reactive groups introduced for subsequent grafting onto the polysaccharide,[17,18] or copolymerization of monomers with a preliminarily activated or modified polysaccharide.[19–22] Copolymerization of monomers with unsaturated polysaccharide derivatives seems to be the most convenient method as it allows regulating the amount of functional groups introduced into SA and, hence, the number of binding sites of synthetic polymer chains with SA. Besides, the latter way avoids a decrease in the molecular weight of polysaccharide, which occurs during activation or modification of SA.

The aim of this work was to create thermosensitive hydrogels based on synthetic polymer poly(*N*,*N*-diethylacrylamide) (PDEAAm) and natural polysaccharide SA with a controllable lower critical solution temperature (LCST) and to study the possibility of their use as a drug carrier. The hydrogels with LCST have been synthesized by copolymerization of SA unsaturated derivative (MSA) and DEAAm in the presence of *N*,*N*′-methylenebisacrylamide as the crosslinking agent. Monomer MSA was obtained by the reaction of SA with glycidyl methacrylate (for details, see Online Supplementary Materials). The compositions and physical-chemical properties of the copolymerized hydrogels obtained in comparison with the two-component mixed hydrogel PDEAAm–SA and the homopolymer PDEAAm are presented in Table 1.

The presence of SA in the mixed hydrogel seems not to affect the LCST value that remains almost the same as for the hydrogels based on homopolymer PDEAAm. In contrast with this type of hydrogels, the network structure of hydrogels obtained by copolymerization of MSA and DEAAm allows an adjustment of

Table 1 Compositions and physical-chemical properties of the hydrogels.

Sample	Initial reaction mixture composition (wt%)			Hydrogel composition (wt%)[a]			SR[b]	LCST[c]/°C
	DEAAm	SA	MSA	DEAAm	SA	MSA		
PDEAAm	100	–	–	100	–	–	66 ± 3	30 ± 0.5
PDEAAm–SA	83.2	16.3	–	83.7 ± 4.2	16.2 ± 0.8	–	38 ± 2	31 ± 0.5
PDEAAm–MSA	84.0	–	15.5	84.8 ± 4.2	–	15.2 ± 0.7	41 ± 2	38 ± 0.5

[a] The hydrogel composition determined by elemental analysis. [b] Swelling degree (swelling ratio, SR) of the gels in relative units was determined from 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. [c] The LCST was determined as described in refs. 23 and 24. For details, see Online Supplementary Materials.

the LCST. The scanning electron microscopy (SEM) data reveal differences in the structure of the gels obtained by the two methods, namely, polymerization of DEAAm in the presence of SA with subsequent crosslinking SA by calcium ions and copolymerization of DEAAm with an SA unsaturated derivative. The structure of mixed gels [Figure 1(*a*)] is sparser, with many large pores. The gels obtained by copolymerization [Figure 1(*b*)] are more structured and we can trace the presence of two types of networks in the SEM imagies.

The LCST value of the copolymerized hydrogels increases significantly and reaches 38 °C, which corresponds to physiological values. It should be noted that the values of the swelling degrees of hydrogels containing a similar amount of alginate, but obtained by two different methods, were almost the same.

To elucidate the possibility of using thermal sensitivity as a driving force for drug release, we studied the kinetics of the drug lidocaine hydrochloride (LD) release from hydrogels in phosphate buffer saline (PBS) at pH 7.4 (for details, see Online Supplementary Materials). The experiments on drug release from the copolymerized hydrogels with modified alginate PDEAAm–MSA were carried out at room (23 °C) and physiological (37 °C) temperatures. The dependence of the LD release rate from the hydrogel on the incubation temperature is shown in Figure 2. Indeed, heating the hydrogel above the LCST results in a conformational transition of macromolecules of hydrogels and a decrease in their swelling degree, which accelerate the drug release rate because of LD ejection from the carrier volume.

In conclusion, the results obtained allow us to control the LCST of the gels and consider the synthesized hydrogels PDEAAm–MSA as a basis for the development of drug carriers with a temperature-controlled drug release rate.

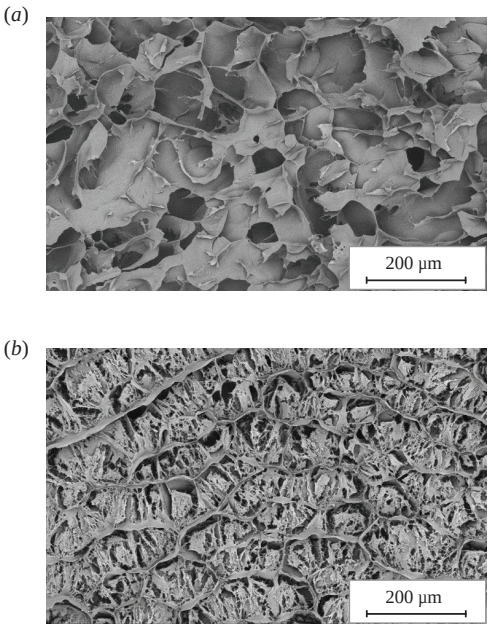


Figure 1 SEM images of (*a*) the mixed gel PDEAAM–SA and (*b*) the copolymerized gel PDEAAm–MSA.

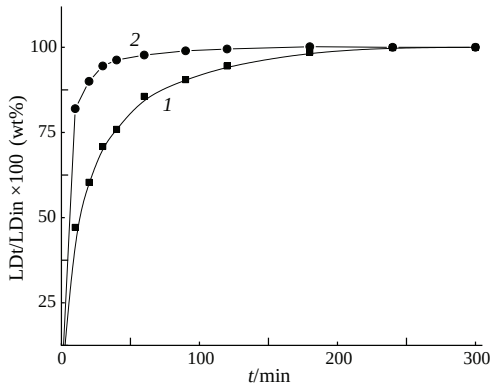


Figure 2 Kinetics of the LD release from the PDEAAm–MSA hydrogel in PBS at pH 7.4 and temperatures above and below the LCST: at (*1*) 23 °C and (*2*) 37 °C. LDt is the current amount of LD (mg) in the solution, LDin is the initial amount of LD (mg) in the gel sample.

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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.2023.10.020.

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