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Structure and properties of hydrogels based on sodium alginate and synthetic polyacids

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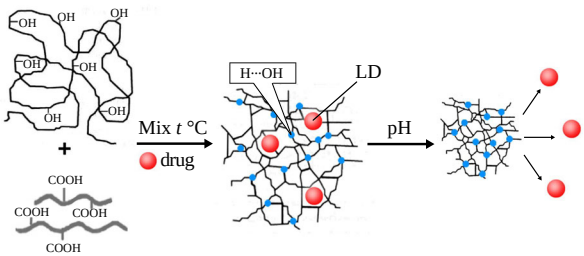
Hydrogels based on interpolymer complexes of sodium alginate and different synthetic polyacids were prepared, and the effect of structure and composition of the complexes on their properties was studied. The microstructure of the hydrogels was investigated by SEM and AFM to understand correlations between hydrogel structures and their behaviors and properties. The hydrogel surfaces were influenced by the polyacid structure and gel preparation method. The hydrogel morphology, swelling, and drug release rate were discussed.



Keywords: hydrogels, polyelectrolytes, sodium alginate, maleic anhydride copolymers, hydrogen bonds, scanning electron microscopy, atomic force microscopy, drug delivery systems.

Hydrogels, soft materials with a porous structure that mimic the properties of biological tissues and can absorb and retain large amounts of water, are widely used in biomedicine as delivery vehicles for drugs, cells, genes, or proteins and as tissue scaffolds.[1,2] The properties of hydrogels can be changed widely with the use of different polymers and a variety of methods for binding macromolecules into networks.[3–8] The development of gels capable of changing their properties under the influence of external factors, so-called smart systems, attract special attention. These systems can be obtained from polymers with properties depending on external conditions (pH, temperature, and irradiation) or formed by networks whose stability is controlled by binding.[9–13] Sodium alginate (SA), a non-toxic, biocompatible, and biodegradable natural polysaccharide, which bears hydroxyl and carboxylate groups in each unit, can be used for preparing hydrogels, micro- and nanoparticles based on SA. Interaction of SA acidic groups with multivalent cations results in the formation of salt bond networks, so-called physical gels.[14–16] However, the gels have heterogeneity and low mechanical strength, which significantly narrows a range of their applications. Covalent cross-linking of polysaccharide molecules provides stable SA gels. However, they require preliminary modification of alginate for introduction of functional groups capable of forming covalent bonds between SA macromolecules[17–19] or use of cross-linkers to react with acidic or hydroxyl groups of SA. Both methods significantly complicate the preparation of hydrogels because of additional stages: modification of an initial polymer and gel purificaton to remove unreacted components. Hydrogels based on polymer mixtures can be an alternative to stable hydrogels with the networks formed by hydrogen, ionic, or hydrophobic bonds. This approach seems very promising because it allows one not only to avoid the difficulties of obtaining covalently cross-linked gels but also to obtain structurally uniform and stable gels.

Previously,[20,21] we obtained hydrogels based on the interpolymer complexes of SA and a number of synthetic polyacids, hydrolyzed copolymers of maleic anhydride with methyl vinyl ether (MVEMA**)** and maleic anhydride with divinyl ether **(**DIVEMA**)**, and polyacrylic acid. According to Fourier transform IR-spectroscopic data, hydrogen bonds between the hydroxyl groups of SA and the carboxyl groups of the polyacid made the main contribution to the hydrogel formation. The hydrogen bonding was largely determined by the polyacid nature and the temperature of gel treatment, and it differed in the number of water molecules involved in H bonds. The applicability of the gel as a drug delivery system was demonstrated based on an example of the drug lidocaine hydrochloride (LD). However, the gel morphology was not studied, while the surface roughness and pore size and volume are responsible for the transport characteristics of gels, and they are decisive factors for designing systems for diagnostics, therapeutics, drug delivery, and cell encapsulation.[22–26] Microscopy techniques are widely used to examine hydrogel morphology and determine pore sizes.[27]

The aim of this work was to study the gel structure by scanning electron microscopy (SEM) and atomic force microscopy (AFM), to reveal the dependence of the film morphology on the polyacid, and to establish the relationship between the gel structure and the macro properties.

The hydrogels were prepared by mixing aqueous solution of SA and polyacids with further drying the mixtures at room temperature (for details, see Online Supplementary Materials). Some of the films were thermally treated at 80 °C for 24 h to improve gel stability and strength according to published data.[28] For example, SA/MVEMA/80 designates a gel sample with the weight ratio SA/MVEMA = 1/1.7 and a film treatment temperature of 80 °C.

The strength and stability of gels based on interpolymer complexes and swelling ratio (SR) values (see Online Supplementary Materials for details) are largely determined by a ratio between components. Previously,[20] we found that an increase in the fraction of a polyacid in gels based on SA and polyacids leads to the formation of a denser cross-linked

network, and the SR of the gels decreases. However, it is well known that the maximum binding of components ensuring optimal properties of the complexes is achieved at certain component ratios.[29] Most often, these ratios correspond to equimolar or equally charged complex compositions. We studied more thoroughly the effect of the component ratio on the properties of the SA/MVEMA/80 and SA/DIVEMA/80 gel to reveal the polymer interaction features. It was of interest to evaluate the swelling of gels in a solution simulating physiological conditions, a phosphate buffered saline (PBS**)** with pH 7.4, since the compositions are intended to use as drug delivery systems.

An optimal ratio between components was found by studying the dependences of the SRs of the hydrogels and the concentrations of soluble fractions in them (weight loss of gel during the swelling) on their composition [Online Supplementary Materials, Figures S4(*a*),(*b*) and S5(*a*),(*b*)]. The swelling of hydrogels decreased with the fraction of a polyacid in the gel. At the same time, the soluble fractions of the gels reached a minimum at the weight ratios SA/MVEMA = 1/1.7 and SA/DIVEMA = 1/1.3. These weight ratios corresponding to a molar component ratio of 1/2 were chosen for further study (Table 1).

Thermal treatment of the gel films resulted in a decrease in the values of the SR in water. According to TGA data, the amounts of bound water in the SA/MVEMA and SA/DIVEMA gel films upon the thermal treatment became 20 and 46 wt% lower, respectively. As shown earlier by FTIR spectroscopy,[20] a decrease in the water content of gels caused a rearrangement of hydrogen bonds because water occurred in a bound state. This is one of the reasons for a decrease in swelling ratios of gels subjected to thermal treatment. Hydrogels were previously shown to form due to hydrogen bonding without confirming published data that heating at 80 °C resulted in the formation of ester bonds between the carboxyl groups of MVEMA and the hydroxyl groups of hyaluronic acid.[28]

The SR values of thermally treated gels in PBS were lower than those in water by a factor of approximately 2–3 [Online Supplementary Materials, Figures S4(*a*), S5(*a*)]. Such a decrease in these values can be due to the screening effect of a low-molecular-weight salt on the carboxyl groups of polyacids that do not take part in the formation of hydrogen bonds and the partial dissolution of gel components.

The hydrogels were prepared from polyacids with numerous carboxylic groups the charge of which depends on pH. Probably, a portion of the groups not involved in binding can provide the sensitivity of hydrogels to the salinity and pH of solutions.

According to Figure 1, the hydrogels demonstrated noticeable dependences of the SR on the presence of salts and only subtle SR variations with pH.

The use of hydrogels as a basis for drug delivery systems was studied based on an example of the model drug LD, a local anesthetic, which is known for its anti-inflammatory effect and proposed recently for additional treatment of COVID-19.[30–32] The additionally heat-treated gels were chosen for a further release study. According to Figure 2, the release of LD from DIVEMA-based gels occurred most rapidly, and the rate of

Table 1 Water content of the dried gel samples and the SR values upon hydrogel swelling in water for 60 min.

Sample	Water content (wt%)[a]	SR in water (arbitrary units)[b]
SA/MVEMA/23	14 ± 1	37 ± 2
SA/MVEMA/80	11 ± 1	27 ± 1
SA/DIVEMA/23	15 ± 1	27 ± 1
SA/DIVEMA/80	8 ± 1	12 ± 1

[a] The water content of the films was evaluated by TGA (see Online Supplementary Materials). [b] The gel/water ratio was (60 mg)/(100 ml).

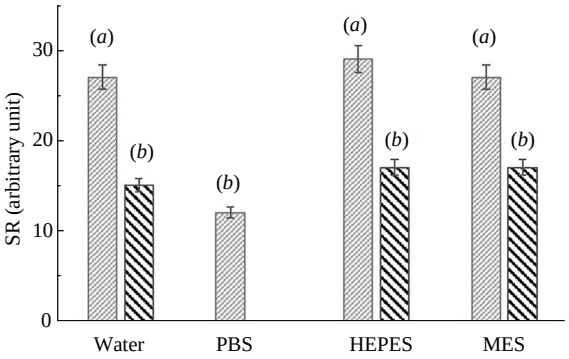


Figure 1 SR values of the SA/MVEMA/80 hydrogel in media with different pH and ionic strengths (PBS, pH 7.4; HEPES, pH 7.2; MES, pH 5.5; and water, pH 6.3) (*a*) without NaCl and (*b*) with NaCl (0.139 mol dm^{-3}).

release from SA/MVEMA was slower; this is consistent with the results obtained earlier for similar gels with other component ratios.[20] The most significant difference was observed at the initial stages up to 20 min, when the equilibrium swelling of the gels in PBS was reached. The rate of the LD release depended on the pH of an incubation medium. Thus, the release of LD was faster from SA/MVEMA hydrogels in acidic media.

An increase in the incubation temperature to 37 °C accelerated the release of LD from SA/MVEMA gels.

The kinetics of swelling of gels with and without the drug LD was studied to explain differences in the rates of LD release from SA/MVEMA/80 and SA/DIVEMA/80 gels. The drug LD influenced the swelling ratio of the gels. Figure 3 shows that the effect depended on the polyacid. Thus, a slight decrease in the SR was observed in MVEMA-based gels containing LD. The SR value of DIVEMA-based gels with LD was higher than that of similar gels containing no drug. Probably, the opposite effects of LD on the SR of gels can be responsible for different drug release rates from the hydrogels. In addition, hydrophobic interactions between the drug LD and the hydrophobic blocks of the copolymer MVEMA, methyl groups, could cause slower rates of LD release.

Hydrogel morphology is responsible for the transport characteristics of hydrogels, and it is a decisive factor for designing drug delivery systems. Figure 4 shows the SEM images of freeze-dried gels. The SA/DIVEMA gels had a rougher structure compared to that of the MVEMA-based gels.

Note that freeze drying changed the original structure of the samples. In order to avoid structure distortion at the stage of sample preparation, AFM with a resolution of 1–5 nm and 3D visualization was used for studying gel morphology (Figure 5) (see Online Supplementary Materials for details).

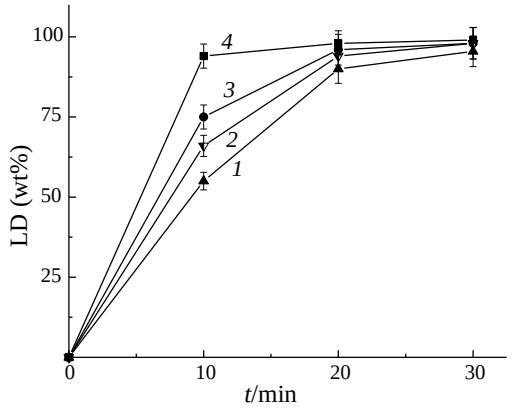


Figure 2 Amounts of LD released from SA/MVEMA/80 gels (*1*) into PBS at 23 °C, (*2*) into PBS at 37 °C, (*3*) into MES at 23 °C, and (*4*) from SA/DIVEMA/80 into PBS at 23 °C.

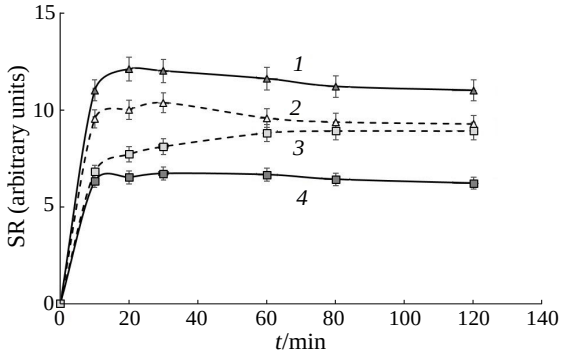


Figure 3 Kinetics of swelling of the hydrogels: (*1*) SA/MVEMA/80, (*2*) SA/MVEMA/80 + LD, (*3*) SA/DIVEMA/80 + LD, and (*4*) SA/DIVEMA/80 (PBS, 23 °C).

An analysis of the 3D images (Table 2) of gel surfaces obtained by AFM shows that the surfaces of all the tested gels were rough, and their morphology had both common and special features. The maximum values of surface roughness and maximum height differences were found in SA/MVEMA films.

The average pore sizes in the gels also depended on the polyacid used for gel preparation and treatment conditions. The pore sizes of MVEMA- and DIVEMA-based gels were 114 and 82 nm, respectively. Thermal treatment of the gels significantly changed the morphological characteristics of gels. The numbers of pores after thermal treatment increased slightly in SA/DIVEMA and significantly, by a factor of more than 2, in SA/MVEMA. The pore sizes decreased in both cases, while remaining smaller in SA/DIVEMA gels.

If the rate of drug release from gels is determined only by the pore size, the rate of release of the DIVEMA-based gels would be minimal. However, according to the experimental data on LD release, the DIVEMA-based gels provided the fastest drug release. This phenomenon may be explained by changes in the gel structure caused by LD. Indeed, according to Table 2, the difference in heights increased for SA/MVEMA and decreased for SA/DIVEMA gels, while the pore numbers decreased in SA/MVEMA gels and increased in SA/DIVEMA gels. The morphology changes were manifested in a decrease in SR values for SA/MVEMA and an increase in the SR for DIVEMA-based gels; it is likely that they caused the difference in the rates of drug release. As mentioned above, an additional factor leading to a decrease in the rate of LD release from MVEMA-based gels could be hydrophobic interactions between the drug and the hydrophobic blocks of MVEMA.

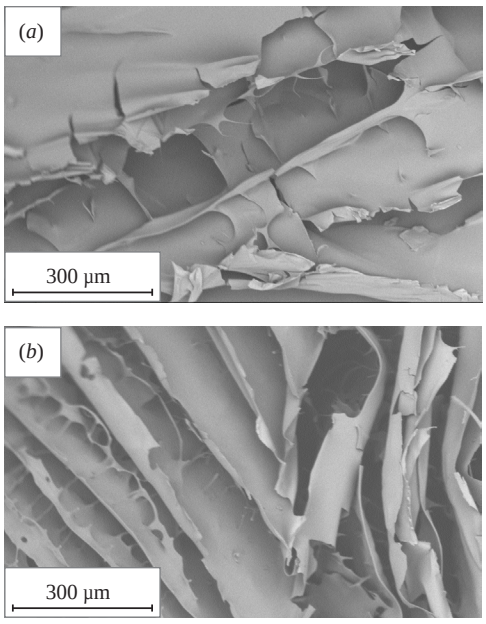


Figure 4 SEM images of the freeze-dried gels: (*a*) SA/DIVEMA/23 and (*b*) SA/MVEMA/23.

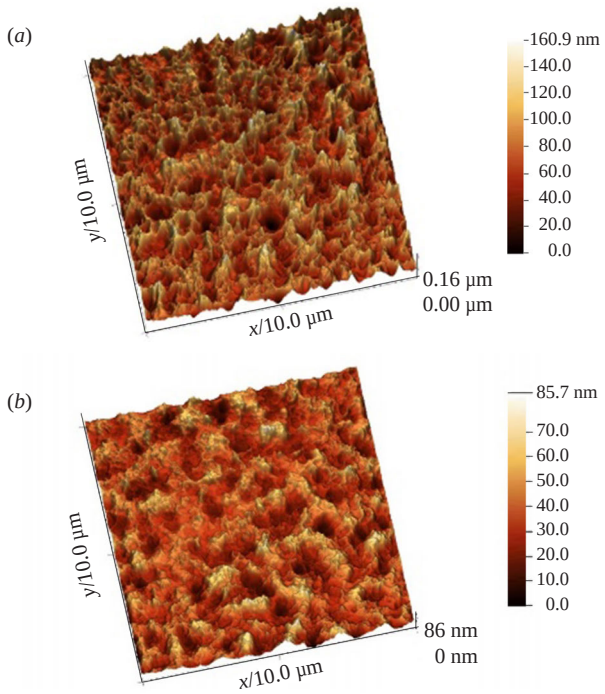


Figure 5 3D AFM images of gels based on different polyacids: *(a)* SA/MVEMA/23 and *(b)* SA/DIVEMA/23. Horizontal and vertical scale bars, 10 μm.

Therefore, a comparison of changes in the macro properties and morphological characteristics of gels makes it possible to explain the dependence of the rate of drug release on the polyacid nature.

Thus, hydrogels based on H-bonded polyacids were obtained and component ratios to ensure optimal hydrogel properties such as stability, soluble fraction, and swelling ratio were found.. A correlation between the morphological characteristics and transport properties of the hydrogels was determined. These gels can be used as drug delivery systems for small molecules with anti-inflammatory and antimicrobial effects.

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Table 2 Gel compositions, preparation conditions, and morphological characteristics of gel surfaces.

Morphological characteristics	SA/MVEMA			SA/DIVEMA		
	23 °C	80 °C	80 °C + LD	23 °C	80 °C	80 °C + LD
Surface roughness/μm	16 ± 1	11 ± 1	8 ± 1	8 ± 1	10 ± 5	6 ± 1
Maximum height difference/nm	161 ± 8	73±4	98±5	86±4	93±5	70±3
Pore number	1293 ± 65	2726±136	1894±94	2018±100	2044±108	2257±112
Mean pore size/nm	114 ± 6	84±4	96±5	82±4	64±3	80±4

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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.2024.04.019.

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