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Anionic Polymer Hydrogel Degradation by Ascorbic Acid

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Abstract—Polymer hydrogel based on sodium 2-acrylamido-2-methylpropansulfonate, covalently crosslinked with *N,N*'-methylenebisacrylamide has been shown to degrade in aqueous ascorbic acid. The hydrogel degradation is induced by chemical interaction of the polymer crosslink and an ascorbic acid oxidation intermediate.

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Polymer hydrogels properties strongly depend on the external factors: temperature [1], medium pH and ionic strength [2], and electrical [3, 4] or magnetic [5] field stimulus. Being highly swollen at equilibrium in aqueous media, hydrogels are soft materials, permeable for low molecular mass solutes, and, thus, biocompatible. These features allow using hydrogels in back-coupling systems (for controlled drug release, in soft robots and actuators), including that implantable into living organisms.

Biodegradable polymer hydrogels can be egested from the body after the desired action, and thus are widely applied in drug delivery systems, for cells immobilization, and in artificial tissues engineering. Usually biodegradable polymers contain heteroatoms in their main chain (typical examples are referred in [6]). In some special cases the carbon-chain polymers also degrade under certain conditions due to easily degradable bonds of the crosslinking agent (peroxides [7] or hydrazones [8]).

Gels based on vinyl monomers covalently crosslinked with *N,N*'-methylenebisacrylamide (BIS) are well studied and are frequently used in the practical applications. Despite the presence of heteroatoms in the crosslinker structure, to the very best of the author's knowledge, such hydrogels have not been yet known to fully degrade under mild conditions; only partial hydrolysis under severe conditions (boiling, drying upon heating) has been reported [9].

In this work complete erosion of the carbon-chain polymer, covalently crosslinked with BIS, under mild conditions in the presence of ascorbic acid is described.

Preliminary observations revealed that the ~1 g of polymer gel sample (crosslinked polymer of sodium 2-acrylamido-2-methylpropanesulfonate, **I**) was completely dissolved within 10–20 h after immersion in aqueous ascorbic acid (2.5 mmol l^{-1}, pH 4).

Further experiments showed that not only gels of homopolymer of **I** was degraded in the presence of ascorbic acid, copolymers of **I** with acrylamide (5 mol % of **I** and more) were degradable as well. Crosslinked polyacrylamide did not degrade under the same conditions. Moreover, other crosslinked polyelectrolytes (polymers of acrylic acid or trimethyl(ethylmethacrylate)ammonium bromide, as well as their copolymers with acrylamide) were not degradable. The erosion process was pH-dependent: degradation of **I** (co)polymers was not observed in aqueous sodium ascorbate (pH 9).

Those qualitative results led to conclusion that of all the examined polymer hydrogels, BIS-crosslinked (co)polymers of **I** were exclusively degradable in the presence of ascorbic acid, acidic medium being the necessary condition.

The ability of sulfonic polyelectrolyte gel to uptake the cationic dye Rhodamine 6G and to release it upon the sample erosion was taken as advantage to quantify the degradation process. In the additional experiment, it was shown that at equilibrium the dye was primarily located in the gel phase (depending on the conditions, the ratio of the dye concentrations in the gel phase and in the surrounding aqueous medium was 50 to 200).

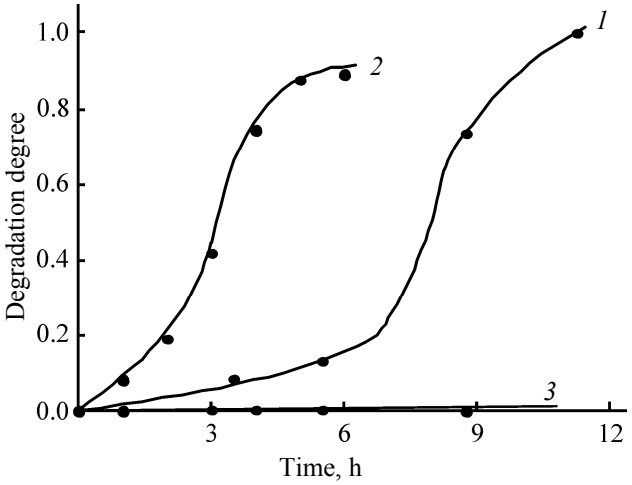

Fig. 1. Hydrogel degradation by ascorbic acid solution (gel: homopolymer of **I**, 3 mol % of the crosslinker; T = 45°C, 2.5 mmol l^{-1} of ascorbic acid, pH = 4). (*1*) freshly prepared ascorbic acid solution; (*2*) ascorbic acid solution incubated during 6 h at 45°C prior to experiment; (*3*) ascorbic acid solution incubated during 2 weeks at laboratory temperature prior to experiment.

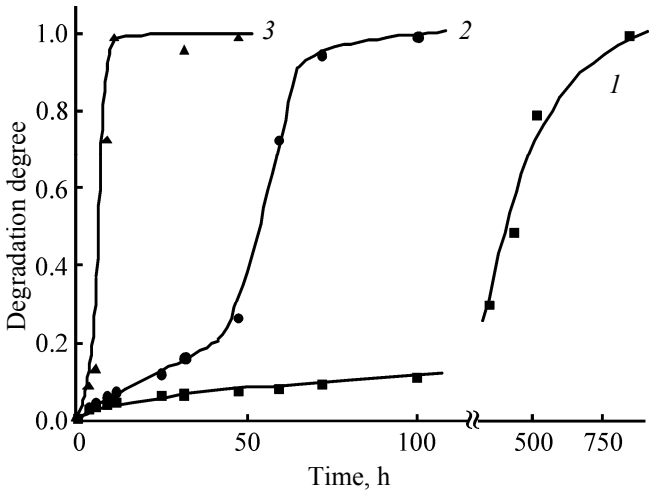

Fig. 2. Hydrogel degradation by ascorbic acid solution (gel: homopolymer of **I**, 3 mol % of the crosslinker; 2.5 mmol l^{-1} of ascorbic acid, pH = 4) at different temperature: (*1*) 6°C, (*2*) 20°C, and (*3*) 42°C.

When used in the kinetic studies, the equilibrium swollen sulfonic crosslinked polymer samples contained about 1–3% of Rhodamine 6G with respect to their sorption capacity (~10^{-5} mol of the dye per 1 g of the swollen gel, exact value being dependent on the polymer composition and swelling). Thus, most of the ionic groups of the polymer were not bound in the complex with the dye. Upon immersion of such sample in aqueous ascorbic acid, the gel degraded, and Rhodamine 6G was released in the surrounding solution. With citric or hydrochloric acid (both did not induce the gel degradation) used instead of ascorbic acid, at pH 4 no more than 1% of the dye was released; furthermore, the optical density of Rhodamine 6G solution, both in the presence and in the absence of ascorbic acid, was found constant within a week. This concluded that the increase of the optical density (at 526.5 nm) of the solution surrounding the sample could be only due to erosion of the sample. As the dye was homogeneously distributed within the gel, the dye concentration in the surrounding solution was proportional to the volume of the degraded piece of the sample.

Typical kinetic curves of the dye release (in the form of optical density of the solution with respect to that after complete degradation of the sample as function of time) are shown in Fig. 1. Curve *1* depicts the gel degradation with the freshly prepared ascorbic acid solution; curve *2* shows the degradation of the gel with the ascorbic acid solution incubated during 6 h at 45ºC (temperature of the successive degradation experiment) prior to kinetic measurement; curve *3* shows the same measurement results, but the ascorbic acid solution has been incubated for 2 weeks prior to kinetic experiment.

Figures 2 and 3 show the effect of degradation temperature and the polymer crosslinking density, respectively, on the degradation kinetics.

At the kinetic curve of the hydrogel degradation induced by freshly prepared ascorbic acid solution (Fig. 1, curve *1*) the induction period was observed; at the initial stage, the dye release was quite slow. During the first 5.5 h of the experiment only 10% of the dye was released from the gel sample. Then the dye release was noticeably accelerated, and further 60% of the dye was released within 3 h; the degradation was complete after 12 h from the start.

The observation of induction period showed that the crosslinked polymer degradation was not a single-stage process. The induction period could be because ascorbic acid should have been accumulated in the gel in certain threshold concentration in order to induce the degradation. Also, ascorbic acid is known to be oxidized by dissolved oxygen, the final product being oxalic acid [10]; if the gel degradation was induced by one of the ascorbic acid oxidation product, the induction period should have been observed as well.

From the induction period dependence on temperature (Fig. 2), the effective activation energy of the rate-limiting step could be estimated: 65±5 kJ mol^{-1}. As the typical activation energy of monosaccharides diffusion was of 15–20 kJ mol^{-1} [11], the limiting role of ascorbic acid diffusion in the crosslinked polymer degradation process was doubtful.

The suggestion of the polymer gel erosion induction by one of ascorbic acid oxidation product was directly confirmed by the data presented in Fig. 1. Degradation of the gel started immediately (curve *2*) after the sample immersion in the ascorbic acid solution incubated during 6 h (that being approximately equal to the induction period of degradation with the freshly prepared solution, curve *1*). The solution of ascorbic acid incubated till its complete decay (as monitored by UV spectral changes) did not degrade the gel at all (curve *3*). Thus, it was some intermediate of the ascorbic acid oxidative decay that induced the degradation of the studied crosslinked polymer. Likely, due to that, the degradation did not occur in the alkaline medium, other conditions being the same: with increasing pH the ascorbic acid oxidation accelerated [12] and its intermediate could not noticeably affect the gel sample.

Data in Fig. 3 confirmed that the BIS crosslinks were the sites of the ascorbic acid attack on the polymer. Indeed, it is known that ascorbic acid oxidation intermediates are of radical (or anion-radical) nature [12], and the methylene protons adjacent to amide nitrogen are extremely labile and easily interact with various radicals [13].

Elucidation of the detailed mechanism of BIS-formed crosslink requires additional structural studies, and is out of scope of this brief report. Furthermore, the role of sulfonic groups of **I** in the degradation processes is not completely clear. Probably, such specific chemical environment stabilized some unstable ascorbic acid decay intermediate and thus allowed its attack on BIS crosslink, otherwise impossible due to short lifetime of the reactive particle. It is also possible that the sulfonate group deprotonated some neutral radical particle to form more reactive anion-radical form [12].

Even though the detailed mechanism of degradation is not yet clear, the observed degradation of the charged hydrogel by biologically active ascorbic acid under mild conditions may be applied in the back-

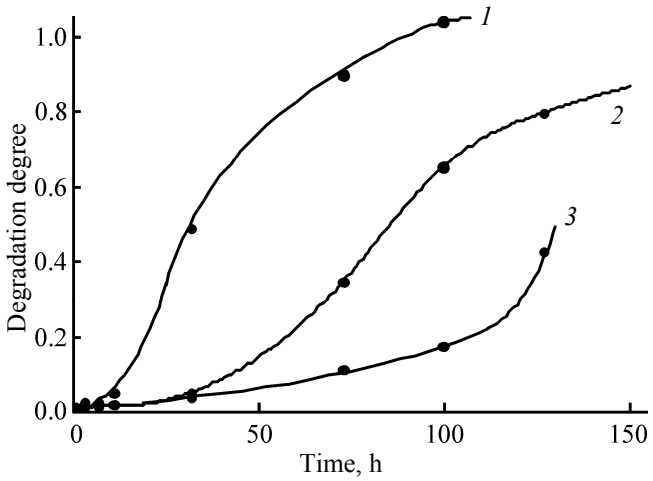

Fig. 3. Hydrogel degradation by ascorbic acid solution (gel: homopolymer of **I**; T = 45°C, 2.5 mmol l^{-1} of ascorbic acid, pH = 4) at different crosslink density, crosslinker (mol %): (*1*) 3, (*2*) 4, and (*3*) 5.

coupling systems of drug release, or in scaffolds for artificial organs fabrication.

EXPERIMENTAL

The studied crosslinked polymers were prepared from the following monomers: sodium 2-acrylamido-2-methylpropanesulfonate **I** (obtained via neutralization of the corresponding acid), acrylamide, acrylic acid, trimethyl(ethylmetacrylate)ammonium bromide, *N,N'*-methylenebisacrylamide BIS. Acrylamides were purified by recrystallization from chloroform, acrylic acid was distilled under reduced pressure, and other chemicals were used as received.

Polymerization was conducted in the aqueous (10 wt %) solution, BIS fraction in the monomers mixture was 1 to 5 mol %. The reaction was initialed with ammonium persulfate at 40°C. After the polymerization (12 h), the obtained product was washed several times with excess of water to remove unreacted monomer, sol fraction, and other admixtures.

The degradation rate was determined by tracking the immobilized dye Rhodamine 6G release (photometry at 526.5 nm). Cubic ~1 g samples were used in kinetic experiments.

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