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Termosensitive and mucoadhesive hydrogels based on modified alginate as drug carriers

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High viscosity SA J61887 (Alfa Aesar), glycidyl methacrylate (Acros Organics), sodium hydroxide, ethanol were used without further purification. MSA was synthesized according to a modified method described in 22. The product structure was characterized by NMR spectroscopy.

^{1}H NMR spectra of solutions SA and MSA in D_2O were registered on a VNMR 400 spectrometer (Varian, USA) with operating frequency of 400 MHz on ^{1}H cores and 100 MHz on nuclei ^{13}C. Chemical shifts were taken relative to TMS.

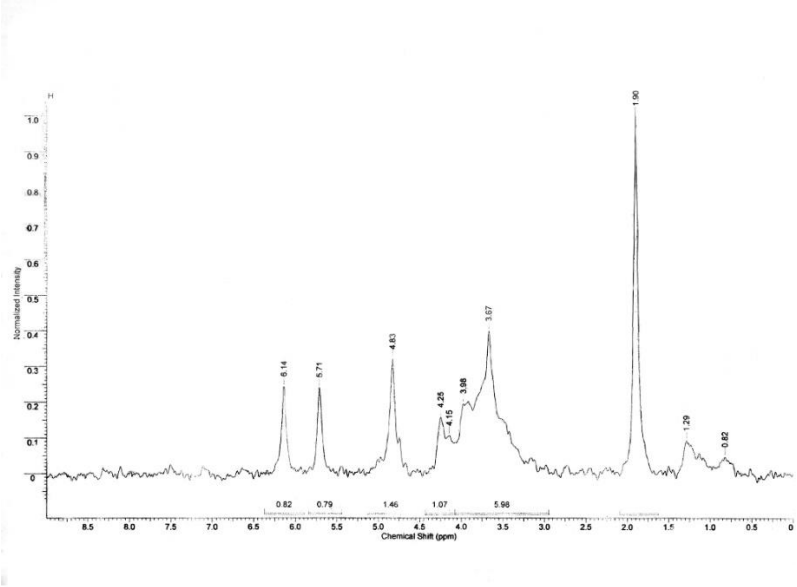

Figure S1 ^{1}H NMR spectrum of MSA.

The percentage of double bonds (DM%) was calculated using the formula below, where *Ha* represents integral intensity of proton signal in the GMA methyl group (δ 4.25 ppm), *HA* represents integral intensity of proton signal in the alginate backbone (δ 3.0÷4.15 ppm).

$$DM\% = \frac{Ha}{Ha + HA} \times 100$$

The DM% of MSA was 15 (mol%) according to ^{1}H NMR spectroscopy data.

Elemental analysis was performed on a CHNS Flash 2000 (Thermo instrument).

Table S1 Elemental analysis data of the gel samples.

Sample	C, (wt%)	H, (wt%)	N, (wt%)
PDEAAm	64.51±3.22	10.06±0.50	10.78±0.54
PDEAAm-SA	65.0±3.25	10.40±0.52	10.95±0.55
PDEAAm-MSA	60.07±3.0	9.59±0.48	9.41±0.47

SEM images were taken on Thermo Phenom XL G2 (Thermo Fisher Scientific, Netherlands).

Synthesis of hydrogels with LCST

N,N'-Methylenebisacrylamide (MBA, Acros Organics), ammonium persulfate (APS, Applichem), *N,N,N`,N`*-tetramethylethylenediamine (TMEDA) all analytical grade were used without further purification. DEAAm (Sigma Aldrich) was bidistillated in a vacuum at 86 °C. Thermosensitive PDEAAm-MSA hydrogels were prepared by copolymerization of DEAAm (4.4×10^{-1} mol dm^{-3} in reaction mixtures), MSA (6.73×10^{-3} mol dm^{-3}; 1.43×10^{-2} mol dm^{-3}; 2.06×10^{-2} mol dm^{-3}; 4.2×10^{-2} mol dm^{-3} and 5.19×10^{-2} mol dm^{-3}) in a presence of the crosslinking agent MBA (2.2×10^{-3} mol dm^{-3}) in water under conditions of redox initiation: TMEDA (5.6×10^{-3} mol dm^{-3}) and APS (3.7×10^{-3} mol dm^{-3}). The system was degasified in order to remove oxygen from the solutions before polymerization. Duration of polymerization was 24 hours at ambient room temperature. The gels were washed in 100 times the volume of water for 5 days with three daily water changes and stirring at 200 rpm.

One-component gels based on DEAAm were prepared similarly but without the addition of MSA. The component content in the gel samples was estimated from the results of elemental analysis.

Determination of the LCST value of the gels.

A weighed portion of freeze-dried hydrogel was poured with 100 times the volume of water and kept at room temperature for 24 hours until equilibrium swelling was reached. The container with the gel was fixed in a thermostat and incubated at required temperature. The hydrogel was removed from the solution, the gel surface was wiped with filter paper to remove the residual water, and the sample was weighed. A gravimetric protocol was used within the temperature range: 23°C - 45°C, increasing the temperature every 15 min by 1°C. The equilibrium swelling degree (SR) for each temperature was calculated as described above. The gel LCST values were found using the dependence [Figure S2] of equilibrium SR versus temperature. The perpendicular dropped to the X-axis from the middle of the linear section enclosed between two horizontal lines on the graph corresponded to the LCST value.

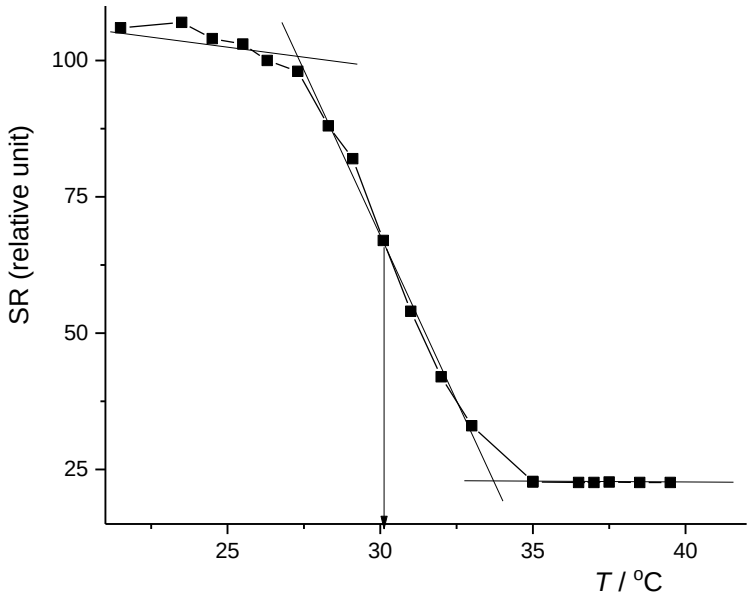

Figure S2 Temperature dependence of SR of the gel PDEAAm.

The swelling degree (SR) (or 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 gel respectively. The sample of freeze-dried gel was immersed in water excess for 24 hours to reach equilibrium swelling, and then the swollen sample was removed from liquid, the surface was wiped with filter paper, and weighed.

LD (Spectrum, USA) was used as received. For the introduction of LD into gels, freeze-dried samples were incubated in 5 (wt%) LD aqueous solutions for 24 hours. The gels were removed from the solution, the residual solution was removed from the gel surface, and then swollen hydrogels were used in drug release experiments under physiological conditions - phosphate buffer saline (PBS), pH = 7.4; 0.9 (wt%) sodium chloride, at two temperatures, room (23°C) and physiological (37°C). The LD concentration was determined by UV spectroscopy on a Specord M-40 instrument (Carl Zeiss Jena, Germany) according to the difference in optical densities of samples taken in experiment with LD-containing gel and experiment with gels without drug. The concentration was calculated from the calibration dependences of the optical density on the LD concentration at a wavelength of 271.4 nm. The results were presented as a dependence of the value $(LD_t / LD_{in}) \times 100\%$ on time, where LD_t is the current amount of LD in the solution (mg), LD_{in} is the initial amount of LD (mg) in the gel.