SYNTHESIS AND PROCESSING OF POLYMERS AND POLYMERIC COMPOSITES

СИНТЕЗ И ПЕРЕРАБОТКА ПОЛИМЕРОВ И КОМПОЗИТОВ НА ИХ ОСНОВЕ

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RESEARCH ARTICLE

Synthesis of thermosensitive copolymers of *N*-isopropylacrylamide with 2-aminoethylmethacrylate hydrochloride

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Abstract

Objectives. *Due to the increasing number of oncological diseases, active research into developing new radiopharmaceuticals is underway. Thermosensitive copolymers have valuable physicochemical properties that can be harnessed to develop therapeutic radiopharmaceuticals for treating solid tumors. The aim of this study was to develop a method for producing thermosensitive copolymers that can find use as radionuclide carriers to create therapeutic radiopharmaceuticals for treating solid tumors.*

Methods. *Using radical copolymerization in polar solvents, we synthesized water-soluble copolymers based on N-isopropyl acrylamide and 2-aminoethyl methacrylate hydrochloride. The resulting copolymers were characterized in terms of molecular composition and hydrodynamic properties using gel permeation chromatography, IR spectroscopy, potentiometry, and viscometry. Changes in optical density during temperature scanning helped determine the phase transition temperature (PTT) of aqueous copolymer solutions.*

Results. *We developed a method for preparing copolymers of N-isopropylacrylamide with 2-aminoethyl methacrylate using radical copolymerization in water and isopropanol with a content of 2-aminoethyl methacrylate hydrochloride in a copolymer up to 23 mol %. We studied how the second comonomer affected the PTT of the aqueous copolymer solutions. An increase in the content of 2-aminoethyl methacrylate in the copolymer caused the PTT to increase. We found that the change in the PTT depending on the content of 2-aminoethyl methacrylate units in the copolymer had a straightforward relationship with its content up to 17 mol %. The use of physiological saline as a solvent led to a temperature decrease of the phase transition by two degrees.*

Conclusions. *The method of producing thermosensitive copolymers by radical copolymerization in isopropanol does not allow creating a radionuclide carrier. Solutions of the obtained low-molecular weight oligomers form coacervate solutions, which will inevitably cause the radionuclide to spread throughout the body. The copolymers obtained by radical copolymerization in water with the content of the second comonomer 2-aminoethyl methacrylate from 10–17 mol % can be used as a radionuclides carrier provided that a physiological solution of sodium chloride is used as a solvent.*

Keywords: *N-isopropylacrylamide, 2-aminoethyl methacrylate, thermosensitive copolymers, radical polymerization, phase transition temperature*

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НАУЧНАЯ СТАТЬЯ

Синтез термочувствительных сополимеров *N*-изопропилакриламида с гидрохлоридом 2-аминоэтилметакрилата

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Аннотация

Цели. *В связи с увеличением числа онкологических заболеваний ведутся активные поиски в разработке новых радиофармацевтических препаратов. В этом аспекте значительный интерес представляют термочувствительные сополимеры, обладающие комплексом ценных физико-химических свойств. Данная работа посвящена разработке метода получения термочувствительных сополимеров, которые могут быть использованы в качестве носителя радионуклидов для создания терапевтического радиофармпрепарата для лечения солидных опухолей.*
Методы. *Методом радикальной сополимеризации в полярных растворителях синтезированы водорастворимые сополимеры на основе N-изопропилакриламида и гидрохлорида 2-аминоэтилметакрилата. Полученные сополимеры были охарактеризованы по составу молекулярным и гидродинамическим характеристикам с использованием гель-проникающей хроматографии, ИК-спектроскопии, потенциометрии и вискозиметрии. Температуру фазового перехода водных растворов сополимеров определяли по изменению оптической плотности от температуры.*
Результаты. *Был разработан метод получения сополимеров N-изопропилакриламида с 2-аминоэтилметакрилатом радикальной сополимеризацией в воде и 2-пропаноле с содержанием гидрохлорида 2-аминоэтилметакрилата в сополимере до 23 моль-звено %. Изучено влияние второго сомономера на температуру фазового перехода водных растворов сополимеров. Увеличение содержания 2-аминоэтилметакрилата в сополимере приводит к смещению температуры фазового перехода, повышая ее. Установлено, что изменение температуры фазового перехода в зависимости от содержания звеньев 2-аминоэтилметакрилата*

в сополимере имеет прямолинейную з ависимость при его содержании до 17 моль-звено %. Использование в качестве растворителя физиологического раствора хлорида натрия приводит к снижению температуры фазового перехода на два градуса.

Выводы. *Метод получения термочувствительных сополимеров радикальной сополимеризацией при использовании в качестве растворителя 2-пропанола не позволяет создать носитель радионуклида. Растворы полученных низкомолекулярных олигомеров образуют коацерватные растворы, что неизбежно приведет к распространению радионуклида по организму. Сополимеры, полученные методом радикальной сополимеризацией в воде с содержанием второго сомономера 2-аминоэтилметакрилат от 10 до 17 моль-звено %, могут быть использованы в качестве носителя радионуклидов только при условии, что в качестве растворителя используются физиологический раствор хлорида натрия.*

Ключевые слова: *N-изопропилакриламид, 2-аминоэтилметакрилат, термочувствительные сополимеры, радикальная полимеризация, температура фазового перехода*

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INTRODUCTION

A modern and effective method of treating cancer is brachytherapy. Microsource introduction inside tumor or near-tumor tissues enables to localize ionizing radiation in the immediate vicinity of cancer cells. The related disadvantages of this method are the complexity and high costs of producing microsources. Around 40 to 80 microsources are needed to treat a disease such as prostate cancer. Their number strongly depends on the severity of the disease [1].

An analog of expensive microsources is the use of polymeric carriers of radionuclides, namely thermosensitive (co)polymers, the aqueous solutions of which have a lower critical dissolution temperature in the temperature range below the physiological temperature of the human body [2]. The aqueous solution of a thermosensitive copolymer, with which the radionuclide is chelated, is introduced into a tumor, undergoes a phase transition and forms a dense gel. The latter acts as a local radiation source. For these purposes, thermosensitive copolymers based on *N*-isopropylacrylamide (NIPA) can be used [3, 4]. The phase transition temperature (PTT) of an aqueous solution of poly-*N*-isopropylacrylamide (PNIPA) homopolymer lies in the range of 32°C, and does not depend on the chain length of the polymer molecule.

The work [5] describes methods of synthesizing polymer-protein thermosensitive conjugates based on PNIPA. The use of these thermosensitive polymer-protein conjugates as radionuclide carriers presents difficulties due to phase transition peculiarities that occur in the pH range between 3.5 and 5.5. In physiological conditions (pH 7.35–7.45), the polymer-protein conjugate cannot form a dense gel and will inevitably spread throughout the body. The authors of [6] developed and patented [7] a method for producing a thermosensitive polymer-protein iodine-containing radiopharmaceutical (RP) with radiochemical purity (RCP) of 95–98%. In this work, we used a polymer-protein conjugate of PNIPA and a globular protein (bovine serum albumin) as a matrix, to the tyrosine groups of which the ^{131}I radionuclide is covalently attached. Related disadvantages include the RP complexity and multistep manufacturing. Purifying RPs from ternary poly-*N*-isopropylacryamide-^{131}I hydrate complexes using the column method increases the RCP, but decreases drug concentration [8].

Study [9] describes an RP based on a thermosensitive carrier, a NIPA-allylamine copolymer with a chelator, and a diethylenetriaminepentaacetic acid (DTPA) added to the amino groups by esterification. A potential disadvantage of this carrier is the low content of DTPA groups, which is due to the lack of a sufficient number of allylamine units in the copolymer, to which DTPA units are attached. In addition, when synthesizing this copolymer, the authors failed to obtain samples of the carrier copolymer with a viscosity average molecular weight M_η > 40 kDa. The reason for this is the chain transfer to the monomer, the so-called “allyl degradation transfer of the chain.” Low-molecular PNIPA

compounds form a colloidal system similar to that of milk dispersion. Therefore, in the drag, the authors had to use a PNIPA polymer thickener that had an average molecular weight $M_\eta \leq 100$ kDa to create a polymeric spatial network [10].

A small number of chelating groups for binding a radionuclide can limit the radiopharmaceutical's maximum efficacy of treating tumors. Increasing the number of functional amino groups in the thermosensitive copolymer should help solve this problem. Replacing the allyl monomer with a methacrylic monomer containing amino groups should increase the molecular weight of the thermosensitive copolymer and eliminate the need for a polymer thickener. 2-Aminoethyl methacrylate hydrochloride (AEM HC) can be used as a comonomer.

The aim of this work is to develop a method of producing thermosensitive copolymers based on NIPA–AEM, with AEM content of up to 23 mol %, study their molecular and hydrodynamic properties, and determine how the number of AEM units in the copolymer affect the phase transition temperature of aqueous solutions of NIPA–AEM copolymers.

EXPERIMENTAL

We used the following reagents in our work: *N*-isopropylacrylamide 97% (*Sigma-Aldrich*, Missouri, USA); *tert*-butyl hydroperoxide 70% aqueous solution (*Sigma-Aldrich*); 2,2-azobisisobutyronitrile (*Vekton*, St. Petersburg, Russia); diethyl ether, chemically pure (*MEDKHIMPROM*, Balashikha, Moscow oblast, Russia); 1,2-dichloroethane, chemically pure (*Ekos-1*, Staraya Kupavna, Moscow oblast, Russia); 2-propanol, chemically pure (*Khimkomplekt*, country of origin: Netherlands); monoethanolamine, chemically pure (*Ekos-1*); methacryloyl chloride, pure (*Ekos-1*). The bidistillate was obtained in a laboratory bidistiller BE-4 (*Livam*, Belgorod, Russia). Methacryloyl chloride was distilled twice before use. Diethyl ether was purified from peroxides [11] and distilled before use. The AEM HC monomer was derived by acylation according to the method proposed in [12] and the yield was 89%. The reaction product was purified twice by recrystallization from dichloroethane. IR spectroscopy helped determine the monomer structure. IR spectra were recorded by an FSM1202 IR Fourier spectrometer (*Infraspek*, St. Petersburg, Russia) in KBr pellets.

Copolymers **1**–**4** (Table 1) were obtained by homogeneous radical copolymerization in 2-propanol. The polymerization was initiated by 2,2-azobisisobutyronitrile. Its concentration in all reactions was the same: 0.024 mol/L. Oxygen was removed by a triple freeze-thaw cycle followed by evacuation after which the ampoules were sealed and thermostated. After a certain time, the ampoules opened, and the contents were precipitated in diethyl ether under vigorous stirring. The formed precipitate was filtered off on a Buchner funnel and dried in vacuum.

Copolymers **5**–**12** (Table 2) were obtained by radical precipitation copolymerization in water. The initial copolymer concentration in all reactions was 0.01 mol/L. Oxygen was removed by blowing argon for 10 min. Then the ampoules were sealed and thermostated. After a certain time, the ampoules opened and lyophilized in a Christ alpha 2-4 LSC plus lyophilizer (*Martin Christ Gefriertrocknungsanlagen*, Germany). Then the samples were dissolved in 10 mL 2-propanol and precipitated into diethyl ether under vigorous stirring. The formed precipitate was filtered off on a Buchner funnel and dried in vacuum.

The quantitative content of AEM HC units was monitored by NH_2 groups using direct and reverse potentiometric titration in ethanol that was previously purified from aldehydes [13]. IR spectrometry helped determine the qualitative structure in KBr pellets in the following absorption bands: 3500–3300 cm^{-1} (ν NH_2), 2974–2887 cm^{-1} (ν CH_3), 1734 cm^{-1} (ν C=O), 1653 cm^{-1} (ν C=O), 1541 cm^{-1} (δ NH_2), 1460 cm^{-1} (δ CH_3), and 1074 cm^{-1} (ν C–O–C).

The copolymer IR band at 1653 cm^{-1} is attributed to the stretching vibrations of the absorption bands (C=O) of the amide group in the associated state. The 1734 cm^{-1} band corresponds to the stretching vibrations of the carbonyl group (C=O) absorption bands of the 2-aminoethyl methacrylate hydrochloride copolymer unit. Furthermore, there is a spectral band at 2380–2840 cm^{-1}, which is characteristic of amino group salt [14].

The intrinsic viscosity of copolymer solutions was determined in a 0.5 M aqueous solution of $LiNO_3$ at 20°C in an Ubbelohde viscometer (*Labtech*, Moscow, Russia). The value of the viscosity average molecular weight M_η of the copolymers was determined using the Mark-Kuhn-Houwink equation [15]. The coefficient values of the PNIPA homopolymer were defined as $K = 4.7 \times 10^{-4}$, $\alpha = 0.61$.

Gel permeation chromatography in dimethylformamide was employed to determine the weight-average (M_w) and number-average (M_n) molecular weights of the copolymers (*Labtech*, Moscow, Russia), which contained 0.1 wt % LiBr. The experiments were carried out at 50°C with the use of a GPC-120 chromatograph (*Polymer Laboratories*, United Kingdom). A differential refractometer was used as a detector. For separation, two PLgel 5 μm MIXED B columns ($M = (5 \times 10^2)$–(1×10^7)) (*Agilent Technologies*, California, USA) were used. The copolymer molecular weight (MW) was calculated

according to calibration measurements conducted against narrow-dispersed polymethyl methacrylate standards.

The PTT values of the copolymer aqueous solutions were determined from the temperature dependence of optical density, obtained by an Agilent 8453 UV-vision spectrophotometer (*Agilent Technologies*). Copolymers were preliminarily purified from HCl with an equimolar amount of 0.1 N KOH solution in water at T = 50°C for 2 h.

Low-molecular compounds were removed by dialysis in water for 2 days in dialysis bags (*Orange Scientific OrDial*, Belgium) with a pore size of 12–14 kDa. The copolymer concentration in the test solutions in all samples was c_{pol} = 1 wt %. The solvents used were double-distilled water and a 0.9% NaCl solution.

RESULTS AND DISCUSSION

Table 1 presents the synthesis conditions and copolymer properties obtained by radical copolymerization in 2-propanol. Statistical copolymers containing AEM HC units from 18.2 to 27.3 mol % were obtained. The low MW values and copolymer conversions stem from the chain transfer to the solvent. Such a low copolymer MW prevents them from being used as radionuclide carriers without using a thickener. Study [16] demonstrated that thermosensitive copolymers based on *N*-isopropylacrylamide with MW $\leq 40 \times 10^3$ are excreted mostly by the kidneys within 48 h. Therefore, the use of copolymers with MW $\leq 40 \times 10^3$ as radionuclide carriers is not appropriate.

Copolymers obtained by radical precipitation copolymerization in water demonstrated higher conversion efficiencies and MW values compared to those of copolymers prepared in 2-propanol. Table 2 presents the copolymerization conditions and MW characteristics. An aqueous solution of copolymer **5** synthesized at a high temperature demonstrated pronounced opalescence compared to that of sample **6** synthesized at 50°C. The opalescence in the copolymer solution most likely indicates macromolecule crosslinking during their synthesis. To this end, all subsequent copolymers were synthesized at 50°C.

An increase in the molar fraction of AEM HC in the monomer mixture results in higher copolymer yield, but decreases its MW. The molecular mass decrease observed with the increased starting monomer concentration is most likely due to the AEM HC ionic effects: that affect the capture of the radical of the growing chain (i.e., prevent chain growth). Study [17] reported similar results. The authors explain this effect by a possible chain transfer to the monomer and the polymer. The study showed that the amino group content in the obtained copolymers is higher than the initial concentrations and does not depend on the conversion rate.

The narrow molecular weight distribution (MWD) that certain samples demonstrate is probably due to fractionation at the isolation and purification stages. The typical MWD curves for some samples are shown in Fig. 1. The M_w values of copolymers **10**–**12** obtained at an initial AEM HC concentration below 0.1 mol/L exceed 10^5. Comparison of copolymers **6**–**9** derived under the same conditions indicates that polydispersity naturally increases as conversion increases. Considering a number of parameters, we conclude that the most optimal samples, which can be recommended for use as RP precursors, are samples **6** and **7**.

The phase transition temperature (PTT) value is a crucial factor in the copolymer use as thermosensitive radionuclide carriers. The human body temperature ranges between 34.4 and 37.8°C [18] and strongly depends on the circadian rhythms of the human body. Proceeding from this condition, the PTT of copolymer aqueous solutions for designing RP should not exceed 34°C. The PTT measurements of aqueous

Table 1. Synthesis conditions and properties of copolymers synthesized in 2-propanol

No.	$[M_1]$, mol/L	$[M_2]$, mol/L	Temperature, °C	Time, h	Conversion, %	$[m_2]$, mol %	$M_\eta \times 10^{-5}$
1	0.72	0.04	50	72	16.3	27.3	0.08
2				96	23.9	18.2	0.15
3			60	72	20.9	20.7	0.12
4			70	72	20.0	21.1	0.11

Note: $[M_1]$ – *N*-isopropylacrylamide, $[M_2]$ – 2-aminoethyl methacrylate hydrochloride, $[m_2]$ – 2-aminoethyl methacrylate hydrochloride units.

Table 2. Synthesis conditions and properties of copolymers synthesized in water

No.	$[M_1]$, mol/L	$[M_2]$, mol/L	Time, min	Temperature, °C	Conversion, %	$[m_2]$, mol %	PTT, °C	PTT 0.9% NaCl, °C	$M_\eta \times 10^{-5}$	$M_n \times 10^{-5}$	$M_w \times 10^{-5}$	M_w/M_n
5	0.9	0.1	15	70	87.1	13.3	33.2	31.0	–	–	–	–
6			15	50	36.5	23.5	–	39.8	11.6	2.6	5.5	2.1
7			37	50	68.5	17.7	33.8	32.8	13.0	1.5	4.3	2.9
8			60	50	92.8	10.9	33.0	31.1	7.7	0.9	3.0	3.5
9			120	50	96.6	10.2	32.9	31.0	7.8	0.8	5.3	6.7
10	0.925	0.075	60	50	60.6	17.7	–	–	–	5.9	12.2	2.1
11	0.95	0.05		50	57.9	9.6	–	–	–	7.4	17.4	2.4
12	0.97	0.03		50	45.9	6.6	–	–	–	6.8	17.1	2.5

Note: $[M_1]$ – *N*-isopropylacrylamide, $[M_2]$ – 2-aminoethyl methacrylate hydrochloride, $[m_2]$ – 2-aminoethyl methacrylate hydrochloride units.

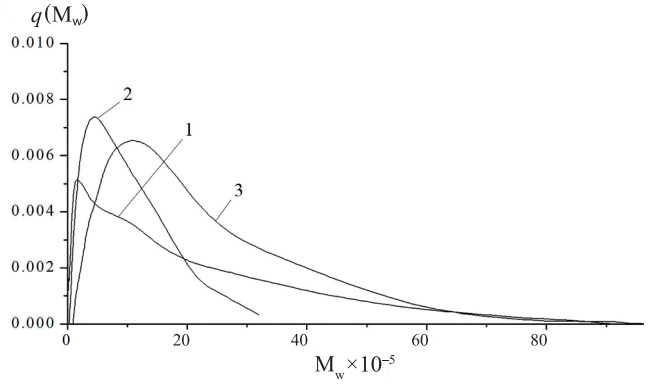

Fig. 1. Molecular weight distribution curves of copolymers: (1) No. **12** ($M_w = 17.1 \times 10^5$); (2) No. **6** ($M_w = 5.5 \times 10^5$); (3) No. **10** ($M_w = 12.2 \times 10^5$); $q(M_w)$ – weight fraction of macromolecules.

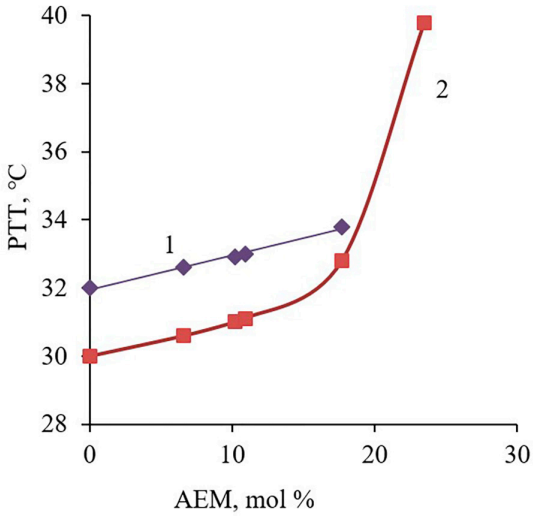

Fig. 2. The dependence of phase transition temperature (PTT) on the content of 2-aminoethyl methacrylate (AEM) in the copolymer: water (1) and 0.9% NaCl (2).

solutions of the obtained copolymers showed that an increase in the AEM fraction follows a linear growth (Fig. 2). When the AEM content in the copolymer exceeded 17.7 mol %, no phase transitions were observed in aqueous solutions. This is probably due to the increased hydrophilic interactions between the increased number of AEM units and water molecules.

Figure 3 shows the turbidity curves of 1% aqueous solutions of a number of copolymers. Organoleptically, copolymer **9** had a dense elastic gel-like structure, while copolymers **7** and **8** formed a coacervate solution in the form of a milk

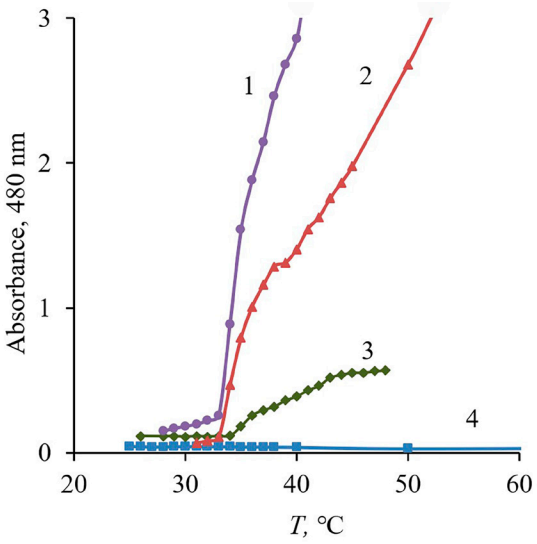

Fig. 3. Turbidity curves of 1% copolymer aqueous solutions: (1) No. **9**, (2) No. **8**, (3) No. **7**, (4) No. **6**.

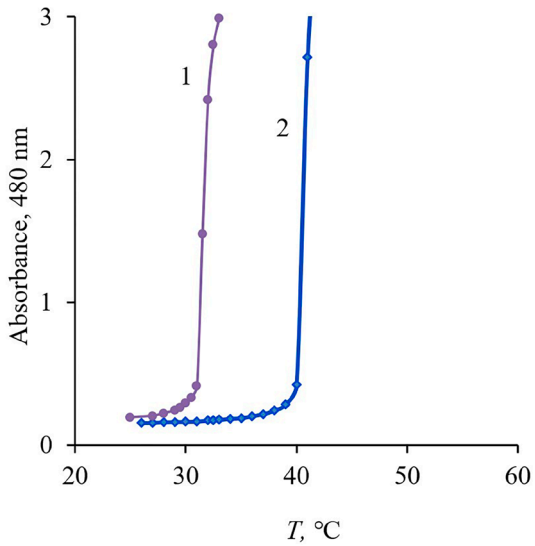

Fig. 4. Turbidity curves of solutions of copolymers prepared in saline: (1) No. **10**, (2) No. **6**.

dispersion. The disperse state of the copolymer after the phase transition does not ensure radionuclide retention in a specific place. The use of saline (a 0.9% NaCl solution) as a solvent causes a decrease in PTT by about two degrees (curve 2 in Fig. 4). Salt molecules are known to be actively participate in the destruction of hydrogen bonds formed between water molecules and macromolecules of both PNIPA homopolymers and copolymers, causing the coil-globule transition. Thus, at a NaCl concentration of 1 mol/L, salt molecules the PNIPA homopolymer to collapse even at room temperature [2]. A characteristic feature of the phase transition in a saline solution is a sharp change in optical density in a very narrow temperature range, indicating the formation of a dense structure of the AEM gel.

CONCLUSIONS

Water-soluble copolymers based on *N*-isopropylacrylamide and 2-aminoethyl methacrylate hydrochloride with different content of amino groups were synthesized by radical copolymerization in water. The resulting copolymers were characterized in terms of molecular composition and hydrodynamic properties using gel permeation chromatography, IR spectroscopy, and viscometry. The study investigated how 2-aminoethyl methacrylate affected the PTT of aqueous copolymer solutions. Increase of the content of 2-aminoethyl methacrylate in the copolymer increases the PTT. The change in the PTT depending on the content of 2-aminoethyl methacrylate units in the copolymer was found to demonstrate a linear relationship up to 17 mol %.

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Authors' contributions

V.R. Duflot – management and scientific consulting;

A.V. Gaivoronsky – planning and conducting research, collecting and analyzing experimental materials, writing the manuscript;

E.I. Lobanova – collection of materials of the experiments.

The authors declare no conflicts of interest.

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