ABSTRACT
on dissertation for the Doctor of Philosophy degree (PhD)
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Abutalip Munziya

Synthesis, characterization and application of new stimuli-sensitive polymers of linear and network structure

The thesis is devoted to the synthesis of new linear and crosslinked copolymers (CPL) based on acrylic acid (AA), N-isopropyl acrylamide (N-IPAA) and 2-hydroxyethyl acrylate (HEA) and hydrophobically-modified amphiphilic polycarboxy betaines containing four different hydrocarbon groups; the study of their physical and chemical properties; the determination of interaction laws of copolymers with medicinal substances (drugs) and the use of polycarboxybetaine as an additive for high-paraffin oils.

Relevance of the research topic.

Recently, special attention has been paid to water-soluble hydrophilic polymers and their cross-linked polymer hydrogels. Researchers are particularly interested in stimulus-sensitive polymers that swell or shrink due to changes in environmental parameters: temperature, pH, ionic strength, electric field, etc. In order for the system to become "smart," a crisis should occur in response to environmental factors, which are based on changes in the conformational state of a macromolecule or their mutual transition, such as a clew - a globule - a polymer that settles from a solution into a precipitate (for crosslinked structures - collapse). Due to the widespread use of such polymers in medicine, agriculture, membrane technology, electronics, environmental problems, etc. it is necessary to improve the technology of their production. In this regard, for the use of one polymer in several industries, it is of particular interest to modify polymers widely studied and already used in production, and to expand their stimulus-sensitive properties.

One of the promising directions for creating stimulus-sensitive materials today is the use of polyzwitterions. Both polyzwitterions and polyampholytes are polyelectrolytes with ionic groups in aqueous solutions. However, in each structural unit of the polyampholyte there is either a cationic or anionic group, and polywitterions are polymers that have both anionic and cationic groups in each structural unit, which gives them special properties.

Therefore, polyzwitterions, due to their unique properties, are used in various fields, including biotechnology, medicine, the oil industry, water treatment, etc.

In the present work, in order to obtain environmental sensitive polymers, copolymers based on acrylic acid, N-isopropyl acrylamide and 2-hydroxyethyl acrylate and hydrophobically modified polycarboxy betaines based on alkylaminocrotonate with methacrylic acid are studied.

Aim of the work: to synthesize new linear and crosslinked copolymers (CPL) based on acrylic acid (AA), N-isopropyl acrylamide (N-IPAA) and 2-hydroxyethyl acrylate (HEA) and hydrophobically modified amphiphilic polycarboxy betaines containing four different hydrocarbon groups; to study their physicochemical properties, to determine

the patterns of interaction of copolymers with medicinal substances (drugs) and to study the possibility of their use as carriers of medicinal substances, as well as the possibility of using polycarboxy betaine as an additive for high-paraffin oils.

In the work, in accordance with the aim of the study, the following tasks were given:

- to determine the optimal conditions for the synthesis of linear and network copolymers based on AA-N-IPAA-HEA and to determine their structure, physico-mechanical, chemical properties using various modern research methods;
- to study the patterns of interaction of stimulus-sensitive copolymers with drugs based on AA-N-IPAA-HEA and determine the antibacterial properties of immobilized hydrogels;
- to synthesize alkylaminocrotonates, to isolate enamine and imine tautomeric forms from its composition, to determine their structure;
- to synthesize hydrophobically-modified amphiphilic polycarboxybetaines containing four different hydrocarbon groups by the RAFT polymerization method and to study their physicochemical properties;
- to study the possibility of using polycarboxybetaines as an additive in order to slow the crystallization of high-paraffin oils.

Objects of study: water-soluble and water-swelling stimulsensitive copolymers based on AA-N-IPAA-HEA; alkylaminocrotonates based on polycarboxybetaines: polymethacrylic acid – octylaminocrotonate P(MAA-OACRO), polymethacrylic acid - dodecylaminocrotonate P(MAA-DACRO), polymethacrylic acid-tetradecylaminocrotonate P(MAA-TACRO), and polymethacrylic acid-hexadecylaminocrotonate P (MAA-HACRO).

Subject of study: physicochemical properties of new water-soluble and water-swelling stimulsensitive copolymers based on acrylic acid (AA), N-isopropyl acrylamide (N-IPAA) and 2-hydroxyethyl acrylate (HEA) and hydrophobically modified amphiphilic polycarboxy betaines containing four different hydrocarbon groups; phase transitions of a copolymer of various compositions; basic laws of complexation of crosslinked copolymers with medicinal substances.

Research methods. The main physicochemical research methods used were Fourier transform IR spectroscopy, ^{1}H NMR and ^{13}C NMR spectroscopy, UV spectroscopy, thermogravimetric analysis, differential scanning calorimetry, turbidimetry, gravimetry, electron microscopy, potentiometry, dynamic laser light scattering, zeta-potential microscopy and scanning electron microscopy.

Source base and research materials consist of 156 sources of literature on stimulsensitive and zwitterionic polymers and hydrophobically modified polybetains and their field of application, as well as in other areas of natural science related to the theme of this study.

Scientific novelty.

For the first time, linear and net copolymers based on acrylic acid (AA), N-isopropyl acrylamide (N-IPAA) and 2-hydroxyethyl acrylate (HEA) were obtained by material initiation by radical polymerization. For aqueous solutions of linear AA-N-IPAA-HEA copolymers, the phase transition at various temperatures and pH of the medium was studied by the turbidimetric method. It was found that an increase in temperature leads to a more intense cloudiness of the system, which also depends on the pH of the medium.

As a result of studying the physicochemical properties of AA-N-IPAA-HEA copolymers by cathetometry, it was found that new polymer hydrogels are characterized by thermally induced collapse, i.e. a sharp change in the ratio of swelling volume with increasing temperature and pH of the medium.

For the first time, in order to use linear and net copolymers of AA-N-IPAA-HEA as drug carriers, the laws of their interaction with medicinal substances were studied. The microbiological activity of hydrogels immobilized with medicinal substances is determined by the degree of decrease in growth of yeast origin fungi *Staphylococcus aureus*. Among the swelling hydrogels in water, it was found that only hydrogels containing 10% of the monomer units of AA in the composition of the copolymers were active, and hydrogels impregnated with solutions of lincomycin and gentamicin exhibit special antimicrobial activity.

For the first time, alkylaminocrotonates were synthesized and the enamine and imine tautomeric forms contained therein were first isolated by TLC and column chromatography, their structure and functional groups were analyzed by ^{1}H NMR and IR spectroscopy. The isolated enamine form was used to synthesize four types of polymers poly(alkylated aminocrotonate-methacrylic acid).

For the first time, hydrophobically-modified amphiphilic polycarboxybetaines containing four different hydrocarbon groups were obtained by the RAFT polymerization method: P(MAA-OACRO), P(MAA-DACRO), P(MAA-TACRO), and P(MAA-HACRO). The molecular weight of the synthesized polycarboxybetaines was determined using gel permeation chromatography, and ^{1}H NMR and IR spectroscopy proved that their structure corresponds to polycarboxybetaines. The isoelectric point of amphiphilic polycarboxybetaines was determined by measuring zeta potentials.

For the first time using TEM, it was established that the structure of self-assembled aggregates of hydrophobically-modified polycarboxybetaines, depending on the pH of the medium, changes from a spherical state through the rod to a tree structure.

In the work, the first obtained hydrophobically-modified polycarboxybetaines were proposed as additives in order to slow the crystallization of high-paraffin oils.

The theoretical significance of the study. It was proved for the first time that by varying the ratio of hydrophobic and hydrophilic units in a macrochain, it is possible to obtain linear and crosslinked copolymers based on AA-N-IPAA-HEA with a temperature-controlled phase transition. For the first time, the enamine and imine tautomeric forms from alkylaminocrotonates were isolated by thin-walled and column chromatography methods and new methods were proposed for producing hydrophobically-modified amphiphilic polycarboxy betaines containing four different hydrocarbon groups from them.

The practical significance of the study. The obtained copolymers based on NIPAAM-HEA-AA could be used as a promising material for creating a macromolecular therapeutic system with controlled drug release, as well as the hydrophobically-modified polycarboxybetaines could be used as additives in order to slow down the crystallization of high-paraffin oils.

The main provisions for the defense:

- copolymerization of hydrophilic monomers HEA, AA with the hydrophobic comonomer N-IPAA allows to obtain a CPL AA-N-IPAA-HEA with pronounced heat-

sensitive and pH-sensitive properties, while the parameters of the thermally induced phase transition can be effectively controlled by varying the ratio of hydrophilic and hydrophobic units in the composition of macrochains and the pH of the medium ;

- the process of immobilization of a drug substance in AA-N-IPAA-HEA hydrogels is accompanied by complexation due to the formation of hydrogen bonds and hydrophobic interaction, and the obtained CPL-drug polycomplexes have antibacterial properties;

- in the synthesis of alkylaminocrotonates, enamine and imine tautomeric forms can be distinguished from its composition;

- the structure of self-assembled aggregates in an aqueous solution of amphiphilic polycarboxybetaines synthesized by the RAFT polymerization method and hydrophobically-modified changes with increasing pH from a spherical state through a rod to a tree structure.

- hydrophobically-modified polycarboxybetaines can be proposed as additives to slow the crystallization of high-paraffin oils.

The main results of the dissertation research are published in 13 scientific papers, including:

- 4 articles in international scientific journals included in the Scopus database, of which 2 articles – in the Langmuir journal of the American Chemical Society of the highest degree of rating (ACS), included in the Thomson Reuters database;

- 5 articles in republican publications recommended by CCSES MES RK;

- abstracts of 4 reports presented at international scientific conferences and symposia.

The structure and scope of the dissertation. The dissertation is presented on 111 pages of typewritten text and includes an introduction, 4 sections, conclusion, 17 tables, 56 figures, a list of used refeces from 156 items.

Based on the results of the dissertation research, the following conclusions are made:

For the first time, linear and net copolymers based on acrylic acid (AA), N-isopropyl acrylamide (N-IPAA) and 2-hydroxyethyl acrylate (HEA) were obtained by radical polymerization. For aqueous solutions of linear AA-N-IPAA-HEA copolymers, a phase transition was studied under various conditions (temperature, pH). It was found that with increasing temperature the turbidity of the system increases, which also depends on the pH of the medium. It was found that an increase in the hydrophobic N-IPAA content in the copolymer leads to a decrease in the phase transition temperature, while an increase in acrylic acid leads to a loss of heat sensitivity due to the ionization of carboxyl groups in it.

For the first time, the basic laws of three-dimensional copolymers were studied using sol-gel analysis and gravimetry methods. It was shown that the degree of equilibrium swelling of hydrogels of AA-N-IPAA copolymers in water and alcohol depends on the amount of AA in the initial monomer mixture. New polymer hydrogels are characterized by thermally induced collapse, which also depends on the pH of the medium. The physicomechanical properties of AA-N-IPAA-HEA copolymers were determined by thermogravimetric analysis, and the morphology of the obtained copolymers was studied by scanning electron microscopy.

For the first time with the aim of using linear and net copolymers of AA-N-IPAA-HEA as drug carriers, the laws of their interaction with medicinal substances have been studied. As medicinal substances, aqueous solutions of lincomycin and gentamicin were used. In the course of the study, it was found that for all samples of water-swelling polymers, additional swelling in a solution of lincomycin was observed in comparison with sodium chloride and gentamicin. The microbiological activity of hydrogels with immobilized medicinal substances is confirmed by the degree of decrease in the growth of yeast origin fungi *Staphylococcus aureus*. Among the swelling hydrogels in water, only hydrogels containing 10% of the monomer units of AA in the composition of the copolymers were found to be active, and the hydrogels soaked in solutions of lincomycin and gentamicin exhibit special antimicrobial activity.

Alkylaminocrotonates were synthesized, and for the first time, the enamine and imine tautomeric forms contained in it were isolated by TLC and column chromatography, and their structure and functional groups were determined by ^{1}H-NMR and IR spectroscopy. The isolated enamine form was used to synthesize four types of polymers poly(alkylated aminocrotonate-methacrylic acid).

For the first time, hydrophobically-modified amphiphilic polycarboxybetaines containing four different hydrocarbon groups were synthesized by the RAFT polymerization method: polymethacrylic acid – octylaminocrotonate P(MAA-OACRO), polymethacrylic acid - dodecylaminocrotonate P(MAA-DACRO), polymethacrylic acid- tetradecylaminocrotonate P(MAA-TACRO), and polymethacrylic acid-hexadecylaminocrotonate P (MAA-HACRO). The structure of the obtained polycarboxybetaines was studied by ^{1}H NMR and IR spectroscopy and it was proved that their structure corresponds to polycarboxybetaines. The molecular weight was determined using gel permeation chromatography, and it was found that Mr is 20,000-30,000 g/mol, and the polydispersity is 1-2. The isoelectric point of amphiphilic polycarboxybetaines was determined by measuring the zeta potential and is equal to pH 1-2.

Using TEM, it was found for the first time that the structure of self-assembled aggregates of hydrophobically-modified polycarboxybetaines varies with the pH of the medium from a spherical state through a rod to a tree structure. Based on the results, it was found that hydrophobic interactions between long hydrocarbon molecules in polycarboxybetaines: P(MAA-OACRO), P(MAA-DACRO), P(MAA-TACRO), and P(MAA-HACRO) can serve as evidence of the formation of a new concept for crystallization of long chain hydrocarbon molecules.

The first obtained hydrophobically-modified polycarboxybetaines were presented as additives to slow the crystallization of high-paraffin oils. A system of decans and paraffins ($C_{24}H_{50}$, $C_{36}H_{74}$) was used as a model of oil. During the study, a change in the precipitation and viscosity of the crystals was observed in the system, which is explained by strong hydrophobic interactions of long-chain hydrocarbons in polycarboxy betaines and a modification of the crystallization of zwitterionic groups. The potential possibility of their use in the oil industry is shown.

Assessment of the completeness for the solution of tasks.

A complete solution of the goals and objectives was achieved by obtaining new stimuli-sensitive copolymers of linear and crosslinked structures AA-N-IPAA-HEA and

hydrophobically-modified amphiphilic polycarboxybetaines, establishing the basic laws of their phase transition, studying the laws of complexation of the obtained copolymer with medicinal substances, and determining the possibility of their practical application in medicine and the use of polycarboxybetaines as additives to slow crystallization of high paraffin oils.

Assessment of technical and economic efficiency proposed in the dissertation. The solutions proposed in the framework of this dissertation can underlie the obtained copolymers based on AA-N-IPAA-HEA, which can be used as carriers of medicinal substances. Hydrophobically modified polycarboxy betaines can be used as additives for high-paraffin oils.