Biologically active polymer nanosystems

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The methods of synthesis of biologically active nanostructured systems based on functional and natural polymers are reviewed. The formation of nanosystems in the process of interaction between synthetic water-soluble polyelectrolytes and amphiphilic ionic surfactants is discussed. The influence of structure and stability of these systems on their biological activity is considered. The complexation between DNA and polycations with the formation of compacted DNA molecules, and the transport of resulting complexes into the cells are discussed. The data on nanostructuring of hemoglobin using polyfunctional crosslinkers and the data on the use of the obtained nanoparticles as oxygen-transporting blood substitutes are summarized. Using nanodisperse silver stabilized with poly(vinylpyrrolidone) as an example it was demonstrated, that transferring silver into nanodisperse state results in widening its bioactivity.

Key words: nanoparticles, polyelectrolytes, surfactants, DNA, polyelectrolyte complexes, hemoglobin.

Introduction

An important task of modern medicinal and pharmaceutical chemistry is the search for new biologically active molecules, as well as the modification of known drugs to improve their therapeutic properties (reducing toxicity, eliminating negative side effects, increasing the duration of action in the body, expanding the range of biological activity, providing for targeted transport to goal organ, *etc.*).

One of the approaches that make it possible to solve these problems is the nanostructuring (nanocapsulation) of drugs *via* an application of biocompatible synthetic or natural polymers. There are several ways of nanostructuring biologically active substances (BAS):

1) the creation of nanoparticles based on biodegradable polymers with immobilized medicinal substances;

2) the formation of nanoscale structures by the interaction of water-soluble ionic polymers (polyelectrolytes) with amphiphilic BAS ions;

3) the synthesis of nanoparticles of biogenic elements and preparation of their nanodispersed composites stabilized by water-soluble, reticulated hydrophilic polymers, and their use as the carriers of BAS;

4) the nanostructuring of natural biopolymers (proteins, nucleic acids) by interchain binding of biomacromolecules or the formation of complexes with synthetic polymers.

Polymeric nanosystems based on polyelectrolyte complexes and surfactants

Classical amphiphilic BAS are ionic surfactants with a positive or negative charge and a hydrophobic radical. The main targets of surfactants in the body are the biological membranes. When bound to the biological membranes, surfactants interact with all membrane components, namely phospholipids and proteins.[1,2] A consequence of this is a disruption in the packaging of the phospholipid bilayer, leading to a change in the physical properties of the membranes (for example, permeability to low molecular weight substances). The disorganization and destruction of the membrane occur by reaching the ratio of surfactant : phospholipid ≈ 1 : 1.8. Cationic surfactants (quaternary ammonium salts and guanidine derivatives showing high bactericidal properties), as well as anionic surfactants from a number of alkyl sulfates, alkylaryl sulfonates[3] are of great importance for medical practice, they are used mainly for sanitary purposes. Broader use of these compounds is limited due to increased toxicity, skin irritation, and other negative side effects. In this connection for example, by modifying the surfactant with synthetic and natural polymers the work is being carried out to eliminate the negative effects.[4,5] Of particular interest are polyelectrolyte complexes of ionic

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 10, pp. 1812—1820, October, 2017.

1066-5285/17/6610-1812 © 2017 Springer Science+Business Media, Inc.

surfactants, which exhibit various types of biological activity. These complexes can be considered as model systems. The study of model systems makes it possible to understand the mechanisms of formation and functioning of complexes of biopolymers with low molecular weight BAS, which are amphiphilic molecules in most cases. The complexes surfactant—polyelectrolyte are capable of reversible dissociation. The equilibrium in the system is established in accordance with the law of mass action, and is shifted toward formation of the complex or dissociation. Many publications have been devoted to the study of the surfactant interaction with macromolecules in aqueous solutions.[6—9] To perform directional tuning of functional characteristics (including biological activity) of the polymer complexes with low molecular weight BAS, it is necessary to know the regularities of the influence of various factors on the stability of these complexes. Quantitative evaluation of the stability of complexes of cationic and anionic copolymers of *N*-vinylpyrrolidone with ionic surfactants in aqueous and water-salt solutions was carried out by polarized luminescence.[8] It has been established that the stability of the polymer—surfactant complexes is significantly influenced by the length (hydrophobicity) of the surfactant alkyl chains, by the degree of filling of the ionic groups of the polymer by surfactant ions (stability increases with filling), and by the distribution pattern (block or statistical) of ionic groups along the polymer chain. An increase in the ionic strength of the solution, depending on the contribution of electrovalent and hydrophobic interactions, can either destabilize the complex or enhance its stability.

Insoluble complexes in the shape of micro- and nanoparticles are formed in the interaction of synthetic linear polyelectrolytes with high density charged groups, owing to their strong hydrophobization. Such insoluble particles and capsules, for example based on chitosan and its complexes with dodecyl sulfate, are used in cosmetics.[10,11]

Copolymers of hydrophilic comonomers (*N*-vinylpyrrolidone and others) with anionic (unsaturated carboxylic acids) comonomers and cationic (vinyl—allylamine, amino(methacrylates), *etc.*)[12] comonomers are used to prepare water-soluble complexes and study the peculiarities of their formation over a wide range of component compositions. The complexes are capable of substitution and exchange reactions, which is important for their functioning as BAS. The transfer of surfactant molecules onto a target (membrane, biopolymer or synthetic polymer containing hydrophobic fragments) is carried out cooperatively (almost instantaneously) that provides for a significant increase in the biological activity along with high local concentration. Thus, in comparison with free surfactants the antimicrobial activity of cationic surfactants increases by a factor 3—5, the number of surfactant molecules bound to a bacterial cell increases by a factor of 6—20, and a decrease in the electrokinetic potential of cells reduces their adhesion to the tissues of the organism and the rate of bacteria penetration into tissues.[5,6]

It should be noted that the complexes are active not only against monocultures, but also against microbial associations consisting of staphylococci and *E. coli*. This is of considerable practical interest, since in clinical practice it is often necessary to deal with associations of different types of bacteria.

Binding of cationic surfactants with ionic copolymers of *N*-vinylpyrrolidone to form micellar-type nanodispersed systems with a particle size of 10—150 nm or more leads to significant changes in their properties. So, the toxicity is reduced by a factor of 1.5—2, and the skin-irritating effect is reduced by a factor of 10. Polymer antiseptic katapol, approved for medical use (reg. No. 91/146/7), was created by optimizing the chemical structure of the carrier polymer, its molecular weight, and supramolecular structure of the complex based on the copolymer of *N*-vinylpyrrolidone with crotonic acid and alkyldimethylbenzylammonium chloride (katamine AB). Katapol nanoparticles actively interact with the cytoplasmic membrane of bacteria, destroy the non-enveloped and enveloped viruses: coronaviruses, rotaviruses, adenoviruses, AH1N1 influenza virus (Fig. 1). They show a high bactericidal and

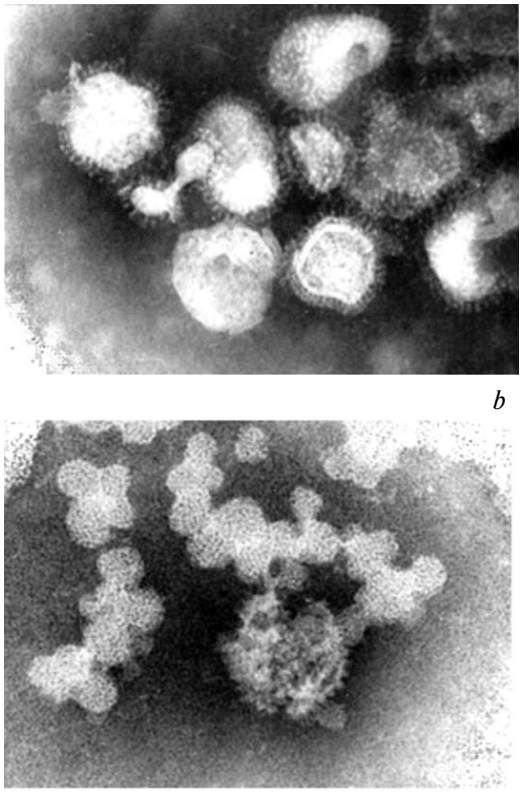

Fig. 1. Interaction of katapol nanoparticles with influenza virus AH1N1virions (C = 0.005%) (*a*) and adenovirus virions (C = 0.65%) (*b*).[13]

virucidal effect at the concentrations of 0.5—0.005%.[13] Other medicinal substances poorly soluble in water (anesthetics, antiseptics, substances with anti-fungal and reparative activity, *etc*.) may be incorporated into katapol nanoparticles, as in nanocontainers.[14,15]

In this way, nanostructured polymer systems have been developed. They possess along with antimicrobial activity, including against antibiotic-resistant microflora, the ability to stimulate wound healing processes,[16] to remove necrotic tissues, and to exert an analgesic effect. This is important for the therapy of the wound infections. These compositions are recommended for the use in medical practice as a part of dressings made of poly(vinyl alcohol) (aseplen films). Katapol is used as an antiseptic in poultry farming, veterinary medicine, food and fish processing industries,[17] as well as in crop production to combat phytopathogenic bacteria and fungi.[18—20]

Depending on the ratio between surfactant molecules and ionic units nanostructures of different types are formed in the reaction of the anionic surfactants (alkyl sulfates, alkyl sulfonates, *etc*.) with cationic copolymers of *N*-vinylpyrrolidone.[21—23] The study of such structures by light scattering and polarized luminescence revealed that depending on the value of the ratio of the polymer ionic groups to surfactant molecules in the solution (γ) the size of a macroion, intramolecular mobility of macromolecules as well as the number of surfactant molecules bound to a macromolecule varies. Thus, for a system consisting of the *N*-vinylpyrrolidone copolymer and *N*,*N*,*N*,*N*-triethylmethacryloyloxyethylammonium iodide, and also sodium dodecyl sulfate as surfactant, when $\gamma > 4.0$ intramolecular mobility of the polymer chains increases. There is a rearrangement of the structure of intramolecular cluster of the surfactant molecules from micelle to pseudolamellar associates.[23] At $\gamma = 0.5$, the macromolecular coil becomes more compact (the size decreases from 60 to 20 nm), and at $\gamma = 4.0$ the size of coil reaches a value of 77 nm. Intramolecular mobility increases almost to the initial level. These structural changes affect the spectrum and the level of biological activity of resulting nanostructures. Anionic surfactants, namely alkyl sulfates and alkylaryl sulfonates, retain their activity against gram-positive bacteria (staphylococcus). The value of the minimum suppressive concentrations is at the level of 50—150 μg mL^{-1} of surfactant, and the toxicity is reduced by a factor of two. Comparative studies of therapeutic properties in *in vivo* experiments on models of purulent inflammation in rats have revealed that the polymer complexes of tetradecyl sulfate lower the seeding of inflammation focus by a factor of ten as compared with low molecular weight surfactants. In addition, they are more effective both in bactericidal action, and in the ability to enhance the action of antibiotics against antibiotic-resistant bacteria. The revealed effects are primarily associated with the creation of a high local concentration of surfactants in nanoparticles and the cooperative transfer of surfactant molecules to the cell membrane. A study of the biological properties of nanosystems obtained on the basis of higher alkyl sulfates and cationic copolymers of *N*-vinylpyrrolidone has shown that they exhibit a wide range of biological activity. In particular, they activate or inhibit proteolytic enzymes, change the permeability of the membranes, and also affect the physiological processes in animals (protein, fat and mineral exchanges).[24]

Thus, the ability to stimulate or slow down the rate of growth of young laboratory animals (rats of diary age up to 1 month) depending on the structure of the alkyl sulfate, the dose, and the structure of the complex was revealed in the study of sodium alkyl sulfates ($ROSO_3Na$) complexes with copolymer of *N*-vinylpyrrolidone and *N*,*N*,*N*,*N*-triethylmethacryloyloxyethylammonium iodide (Table 1).

The efficiency of the complex with $\gamma = 4.0$ was confirmed in the experiments with young cattle.[25] Optimization of the structure led to the creation of a highly effective veterinary drug doxane and fodder additives based on it (doxane-M), increasing the productivity of various farm animals (pigs, sheep, cattle, laying hens, and broilers).[26—28]

High efficiency of the drug is due to the activation of digestive processes in animals, increased digestibility of fodder, as well as increased secretion of endogenous anabolics, in particular, androstenedione and testosterone in bull calves.[28] Along with stimulation of growth, doxane has a neuromodulatory effect, namely, it exhibits adaptogen properties of reflex action, potentiates cardiopulmonary reflex caused by intravenous injection of serotonin.[29—32] In addition, this drug is effective as a treatment for metabolic disorders in young cattle.[33] The con-

Table 1. Influence of the structure of complex polycation—surfactant ($ROSO_3Na$) on the growth of young animals (rats)[22,24]

R	γ^a	Daily dose/mg kg^{-1}	Δm^b (%)	Δl^c(%)
$C_{12}H_{25}$	2.0	11	−8	−13
	2.5	11	0	0
	3.6	7.4	+26	+35
	4.0	7.4	+49	+6.5
	5.0	7.4	+6	+4
$C_{14}H_{29}$	4.0	7.4	0	0
	4.2	22	−10	−14
$C_{16}H_{33}$	4.0	7.4	+24	+34
	4.0	7.4	+26	+39

[a] γ = [surfactant] : [polymer].
[b] Weight gain.
[c] Increase of linear dimensions, length.

sequence of this is a strong antihypoxic, analgesic and anti-shock effect, comparable in efficiency to adenosine triphosphate. The drug enhances the secretion of endogenous neurotransmitters, increases their activity, and also potentiates the action of subthreshold doses of exogenous BASs acting on the central and peripheral nervous systems (ethanol, analgin, hexenal, *etc*.). In this case, the potentiating effect of doxane on neurotransmitters is manifested regardless of the mode of administration, namely, intragastric, intravenous or intraperitoneal. Such effect of doxane on neurotropic substances can significantly reduce their effective therapeutic doses and thereby eliminate side effects. Thus, the modification of known ionic surfactants by forming polymeric nanostructures of different types upon interaction with water-soluble polyelectrolytes (*N*-vinylpyrrolidone copolymers) allows to reduce significantly their negative side effects and produce new types of biological activity that are not specific for them.

Nanostructured systems based on biopolymers

Targeted delivery of foreign genetic material to intact target cells is a promising method for solving the problems of biotechnology, biology, and medicine.[33,34] The construction of gene vectors intended for this kind of delivery is associated with the solution of the problem of compaction of a rigid DNA macromolecules carrying negatively charged phosphate groups. These groups ensure a high charge density of the macromolecule over a wide range of pH values. At the same time, it is necessary to observe the conditions ensuring the preservation of DNA functional properties, namely, a double-helical structure, and protection from the action of the nucleases. The gene vector must penetrate the cell membranes and act as a viral particle transferring modified DNA. The selection of safe and effective vectors for the transfer of genes *in vivo* is one of the topical tasks of molecular biology and the basis for their successful use in medicine.[34] Retroviral vectors, vectors based on DNA viruses, and inactivated viruses are used as carriers.[35—41] However, viral vectors are not widely used due to immunological reactions and the risk of pathological transformation of cells. An alternative to this method is the formation of interpolyelectrolyte complexes (IPCs) of DNA macromolecules with synthetic polymers, where DNA is compacted and protected from nuclease, protonation, and other unfavorable environmental factors. The main problem in creating of the IPC is the selection of a synthetic polymer, a polycation, which should be non-cytotoxic, biodegradable or can be removed from the body, and ensure the reversible compaction of DNA and its transport into the cell. Non-viral gene therapy using synthetic polymers, polycations, has a number of advantages in comparison with other directions. Firstly, the probability of activation of the body immune system and the risk of possible side effects are decreased. Secondly, it is easy to form compact IPCs in the solution as a result of electrostatic interaction of negatively charged phosphate groups of a DNA molecule with positively charged groups of polycation.[42—44] At the same time, IPCs, which are compact nanostructures, are formed due to the cooperative binding of macromolecules. Polycations of various chemical structures, polylysine and its derivatives,[45] polyethyleneimine,[46] polyvinylamine and polyallylamine, polyaminoethyl methacrylates,[47] as well as statistical block and graft copolymers of cationic and neutral hydrophilic monomers,[48,49] and chitosan derivatives,[50] are used to create the IPC with DNA. It has also been proposed to use nanocomposites of silver with polydimethylamine methacrylate, which are able to compact effectively the DNA molecule in solution.[51] This approach opens the possibility of using silver nanoparticles as gene vectors.

The influence of the polycation chemical structure, its molecular weight, the type of the ionic group (primary, tertiary amino group or quaternary ammonium group with various alkyl substituents on the nitrogen atom) on the interaction with DNA, the stability of the complexes and the transfection properties, the efficiency of transport into cell, was studied. It was found that the introduction of hydrophobic alkyl substituents leads to an increase in the intrachain contacts of the polycation macromolecule, a weakening of the interaction with DNA, and a decrease in the transfection activity of the polycation. It should be noted that the IPC DNA—polycation have low cytotoxicity and, given their high degree of transfection of eukaryotic cells, can be used as promising vectors in gene therapy.

The nanostructuring of protein macromolecules in order to give them new properties is of great interest. The nanostructuring of hemoglobin, a protein that performs the gas transport function of blood (reversible transport of oxygen and carbon dioxide), is of practical importance. The development of blood-substituting solutions, capable of performing a gas transport function in the treatment of severe blood loss, remains an actual problem. Until now, the main therapeutic method for massive blood loss was a transfusion of blood or erythrocyte mass. However, a significant reduction in the number of donors creates problems with the provision of blood and its components. Only 1.4% of the population donates blood in Russian Federation. In addition, we should especially note the provision of biological safety associated with the risks of transmission of blood borne infections (hepatitis B and C, HIV infection, syphilis, *etc*.). Most post-transfusion complications are of an immunological nature, since the blood transfusion is essentially a transplantation of the antigenic material to the recipient from the

donor. Another problem is the change in the properties of the blood and its components during storage. The shelf life of the erythrocyte mass in the Russian Federation is 35 days. Artificial blood substitutes that have the ability to transport gases, O_2, CO_2, and NO, are considered as an alternative to donor blood.[52] Developments of the blood substitutes with gas transmission properties have been carried out throughout the world since second half of the last century in two main directions: based on perfluorocarbon emulsions[53,54] and based on hemoglobin.[55,56]

In the 30th of the last century, the ability of hemoglobin to maintain its functions outside erythrocytes was established.[57] This was the impetus for the work on the creation of blood substitutes (oxygen carriers) based on extra-erythrocyte hemoglobin. The advantage of hemoglobin over donor blood is that hemoglobin does not have antigenic properties. However, due to the loss of 2,3-diphosphoglycerate, a natural regulator of oxygen transport, in the case of blood substitutes, the efficiency of oxygen transport significantly decreases (up to 20% of the erythrocyte efficiency). Besides, because of low stability, extra-erythrocyte hemoglobin is converted into methemoglobin, and also dissociates into dimers that leave the bloodstream in 1.5—2 h, irreversibly damaging the kidneys. Therefore, in order to use human hemoglobin as the basis of blood-substituting solutions with oxygen transfer function, the following problems have to be solved: the stabilization of the quaternary structure of the protein, the increase in the size of the protein molecule to increase circulation time in the bloodstream and eliminate the damaging effect on the kidneys, and the improvement of the oxygen transport efficiency. Many researchers have been engaged in solving this problem for several decades already.[55—60] To achieve this goal, various methods are used, namely, the confinement of hemoglobin in the liposomes with a size of 80—100 nm and nanocapsulation,[61] the sorption immobilization of hemoglobin on microdispersed carboxyl mesh polyelectrolytes,[62,63] *etc*. Thus, microparticles with 1—5 μm in size and high content of sorbed hemoglobin (up to 15—20 g per 1 g of sorbent) are obtained using the method of sorption immobilization. They exceed significantly by the efficiency of oxygen transport hemoglobin and approach the efficiency of human erythrocytes.[64] Various methods of chemical modification of hemoglobin, namely intramolecular cross-linking of α- and β-subunits with various bifunctional cross-linking agents to prevent dissociation, have been developed. In particular, pyridoxal phosphate and its derivatives,[65,66] 3,5-dibromosalicylic acid and its derivatives[67] have been used. Such intramolecularly cross-linked derivatives were of 7—9 nm in size, were thermally stable and approached erythrocytes in the efficiency of the oxygen transport. However, because of the small size of the nanoparticles they were accumulated in the kidneys, damaging them, and exhibited other side effects.[68]

Conjugation of hemoglobin with natural and synthetic polymers (with dextran and its derivatives,[69] hydroxyethyl starch,[70] polyethylene glycol,[71] polyvinylpyrrolidone[72]) made it possible to obtain the nanoparticles of 20—80 nm in size, which were characterized by high affinity for oxygen.[55—58]

Polycondensation of hemoglobin with glutaraldehyde and its derivatives is often used. The reaction proceeds in two steps: 1) the fast step consists in the modification of the amino groups of hemoglobin without changing the molecular weight, 2) the slower step leads to the intermolecular cross-linking and the formation of nanoparticles from interconnected hemoglobin molecules of more complex organization than native hemoglobin. Structural and conformational mobility, as well as the functional activity of the hemoglobin should be preserved. For this, it is permissible to modify not more than 15—20% of the available amino groups of the hemoglobin molecule.[73] A multifunctional cross-linker, a derivative of glutamic acid and glutaraldehyde, which serves as a cross-linker and regulator of the oxygen affinity of hemoglobin was used to stabilize the quaternary structure of the protein and improve its gas transport characteristics.[74,75] Nanostructuring of hemoglobin by this method made it possible to balance the formation of intra- and intermolecular bonds, to stabilize its quaternary structure, and to obtain nanoparticles with a size from 10—15 to 60—80 nm with a high local protein concentration. These nanoparticles are close to human erythrocytes by the efficiency of oxygen transport.[76] Such hemoglobin served as a basis for the creation of the blood substitute gelenpol with oxygen transport function, which possesses anti-shock and hemodynamic action and is able to stimulate the hematopoietic functions of the organism.[77] Thus, the drug was successfully developed, clinically tested, and has got permission for clinical use by the efforts of researchers from the Institute of Macromolecular Compounds of the Russian Academy of Sciences and the Russian Research Institute of Hematology and Transfusion. Gelenpol is used to correct hemodynamics in acute blood loss and shock, and as an anti-anemic agent in acute and chronic anemia. The work on the creation of blood substitutes on the basis of nanostructured hemoglobin is actively conducted by foreign scientific centers and companies. Thus, the drug HemAssist was created on the basis of hemoglobin intramolecularly cross-linked with diaspirine.[78] The drug Hemolink® is a human hemoglobin reacted with raffinose to form intramolecularly cross-linked hemoglobin molecules and oligomers with a molecular weight of $(120—600) \cdot 10^3$. However, both of these drugs were withdrawn from the clinical trials because of undesirable side effects. The clinical trials of the Poly-Heme® drug based

on glutaraldehyde-cross-linked hemoglobin tetramers modified with pyridoxal phosphate also failed.[79,80] At present, several blood substitutes based on bovine hemoglobin have been developed. Some of them are in preclinical and clinical trials, while others are already promoted to the markets. Thus, drug Hemopure is a condensation product of bovine hemoglobin with glutaraldehyde.[55] It has been permitted for use by the vital indicators in the USA, it is registered in South Africa, and it is promoted to the Russian market by the company Biotech.[81,82] The composition of this drug includes covalently attached enzymes, namely, catalase and superoxide dismutase. The inclusion of antioxidant enzymes reduces the oxidation of heme iron, facilitates the removal of peroxides and free radicals from the bloodstream. The drug is considered as a promising therapeutic agent used in situations associated with ischemia and the development of oxidative stress in myocardial infarction, stroke, *etc*.

In addition, the same research group developed the drug polyHb-Fg, which is a complex of polyhemoglobin with fibrinogen[83] and has a thrombocyte-like activity. It is believed that this drug will be effective at massive blood loss.

In conclusion, it should be noted that the nanostructuring of extra-erythrocyte hemoglobin of various origins is the main approach in the development of the blood substitutes. To date, more than 20 prototypes of drugs have been created, but so far none of them have been introduced into a wide clinical practice. However, the intensity of research in this direction makes it possible to predict the appearance of blood substitutes based on hemoglobin with gas transport properties in the near future.

Polymer systems of biogenic elements

Polymer composites, containing biogenic elements Ag, Pt, Au, Se, and Cu, have attracted attention recently due to the possibility of using them for the treatment of tumor diseases, bacterial and viral infections, *etc*.[84—86]

In this respect, composites containing silver are of particular interest, since silver has a broad spectrum of antimicrobial activity. Nanodispersed silver stabilized with hydrolysates of gelatin and casein such as protargol and collargol have been used in clinical practice for over a hundred years. However, these drugs have increased toxicity and cause immunological reactions. Therefore, new silver formulations without side effects under application of various water-soluble polymers such as polyvinylpyrrolidone, polysaccharides, polyvinyl alcohol, *etc*. are being developed.[87—92]

Depending on the polymer-stabilizer and the reduction conditions of Ag, nanoparticles of different morphology are formed. They can take the shape of a sphere, pyramids, nanorods, nanowires, *etc*. The shape of nanoparticles affects the antimicrobial properties of nanocomposites. The most active is the composition containing 8 wt.% of Ag nanoparticles with a maximum specific surface area and medical polyvinylpyrrolidone as a stabilizer. It is authorized for medical use under the name poviargol (registration No. 97/167/7). This drug is less toxic by a factor of four than widely used products protargol and collargol, and does not yield immunological reactions. Unlike formulations of ionic silver, poviargol stimulates tissue repair at the epitheliazation stage, as well as humoral immunity, showing the properties of a thymus-independent antigen. This opens the prospect of its practical application in the treatment of immunodeficiency conditions and autoimmune diseases.[92—94] The preparations of nanodispersed silver, namely, poviargol, protargol, and collargol exhibit new types of biological activity by intragastric administration. They increase the body resistance to hypoxia, pain, shock, and also potentate the effect of a number of substances on the central nervous system[93—95] (Table 2).

From a practical point of view, nanodisperse systems that contain proteolytic enzymes, such as chymotrypsin,[95] are attractive as a protective polymer. Such drugs are promising for the treatment of wounds and burns, since along with the antimicrobial effect, they remove necrotic tissues.

The nanocomposites based on copper are of interest between other biogenic elements. They have strong fungicidal effect against a large number of phytopathogens. A reduction of copper ions by $H_4N_2 \cdot BH_3$ in the presence of polyvinylpyrrolidone results in the formation of nanoparticles with a size of 7.6—9.6 nm. However, the disper-

Table 2. Adaptogenic properties of polymer nanodispersed systems with intragastric administration[22,92,93]

Drug	Dose /mg kg^{-1}	τ^a/min	Survival^b(%)	
			I	II
Doxan	10	17.5	52.6	54.0
Poviargol	10	15.2	38.0	65.0
Protargol	15	12.2	43.6	—
	150	13.7	—	—
Collargol	15	15.3	—	—
	150	17.6	—	—
ATP	10	14.9	20.1	—
Control	—	11.3	10.0	0

[a] Lifetime of mice with canned hypoxia. [b] I is the survival of rats after 24 h with hemic hypoxia after administration of 85 mg kg^{-1} $NaNO_2$; II is the survival rate of rats with hypoglycemic shock after the administration of a double lethal dose of insulin.

sions of copper nanoparticles are rapidly oxidized[89] and have low aggregative stability. The attempts to obtain stable nanosystems by synthesizing bimetallic nanoparticles of copper (core)—silver (shell) at an elevated temperature in a nitrogen atmosphere were more successful.[96]

Selenium is also an important biogenic element. It is a part of many enzymes, it interacts actively with free radicals and exhibits antioxidant properties. Deficiency of selenium in the body leads to cardiovascular, oncological, and other diseases. The synthesis of selenium nanoparticles is carried out by reduction of H_2SeO_3 with ascorbic acid. Obtained amorphous selenium nanoparticles with a size of 6—18 nm are coated with a dense polymer layer.[97] Such composites have a lower toxicity than the ionic derivatives of selenium. Therefore, they are more promising for the creation of less dangerous selenium-containing drugs on their basis.

Thus, the modification of widely used ionic surfactants can significantly reduce negative side effects and give these substances new nonspecific types of biological activity. The modification can be carried out *via* formation of polymeric nanostructures of various types in interaction with water-soluble polyelectrolytes, namely, copolymers of *N*-vinylpyrrolidone, the fabrication of compact polyelectrolyte complexes of DNA, intra- and intermolecular cross-linking of hemoglobin using various multifunctional cross-linkers, as well as the synthesis of nanoparticles of biogenic elements in the presence of stabilizing water-soluble polymers.

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Received May 16, 2017