PERSPECTIVES ON CREATING POLYMERIC DRUGS

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Abstract

In this paper, the results of medicinal compound's polymeric forms, classification and principles of their development are discussed. The basic requirements for carrier polymers and polymers with their own biological activity are developed to create low-molecular drugs, their polymer forms and polymers with their own biological activity. Weak biological activity of a number of polyanions has been established as antitumor, immunomodulatory, interferon-inducing, and other activities. However, due to weak biological activity, they cannot be used in practical medicine. This work also considers the molecular construction of medicinal polymers that provide prolongation, selectivity, reduced side effects, preservation of therapeutic concentration in the body, reduced toxicity, and increased specific effects of the drug. The limitations for carrier polymers in molecular construction have been established, as well as in creation of polymer forms of drugs. A list of classes of drugs, for which the creation of their dosage forms is relevant, has been also defined. On the basis of the study results, it was concluded that drug polymers and their possible practical creation are in many cases unique and cannot be achieved with the use of low molecular weight drugs.

Keywords: polymer, drug, biodegradations, cellulose, sodium-carboxymethylcellulose, nanostructured, biological activity

Introduction

The development of polymer science and pharmaceutical industry is of particular importance for the creation of new types of natural and synthetic polymer forms of original preparations and medical products. In the recent years there has been a great deal of large-scale scientific studies in this field of nanotechnology development.

Analysis of chemistry and physical chemistry development, including nanochemistry and nanotechnology, in the creation of original pharmaceutical products, shows that polymeric nanostructured biologically active compounds have a number of advantages, unlike traditional low-molecular drugs. Before proceeding to the peculiarities of polymer forms of drugs it is necessary to consider the main distinctive features of nanopolymer-based drugs from traditional low-molecular medical products [1]. The polymeric form of the drug contains an active principal drug substance (DS) and the dosage form which ensures the penetration of DS into the body.

The effectiveness of the drug is determined not only by the content, structure, and properties of DS but also by its dosage form. Polymeric forms of drugs can be divided into two groups, differing in their biological activity. The first group of DS polymeric forms is the compounds with biological activity determined by their polymer structure, their molecular mass (MM), chain-length distribution, the nature and content of functional groups, and the physical-chemical properties of the macromolecule. The low molecular weight analogs of these polymers in most cases do not possess the biological activity attributed to this type of polymers.

The mechanism of action of this polymer type is not associated with their fragmentation into low molecular weight biologically active parts but is realized due to the properties of macromolecules, in particular to cooperative polymer-polymer reactions between biopolymers of the organism and polymeric forms of a biologically active compound. Their action mechanism is not typical for low molecular drugs. This type of biopolymers (BPs) with "intrinsic" biological activity is related to diversified and also low molecular weight DS.

BPs with “intrinsic” biological activity can be divided into four large groups [2]. DS polymeric forms include polymers that naturally occur in the organism, or “polymer carrier” (PC), and low-molecular or high-molecular DS. Such polymers can be conditionally attributed to the group of “inoculate” type polymers, as in PC overwhelming state the low- and high- molecular medical compounds are chemically attached (grafted) to PC by various chemical bonds: covalent, ionic, coordination, etc. In the second group of polymers in most cases, biological activity is manifested by the grafted fragment.

The biological activity of this group of BPs varies due to the basic principles of carrier polymer molecular design and the low or high molecular weight of DS.

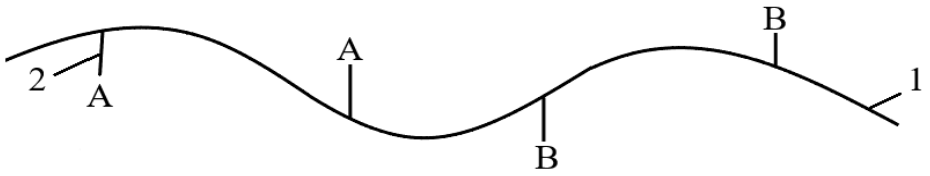


Figure 1. Polymeric forms of drug substances with intrinsic activity [3-6]

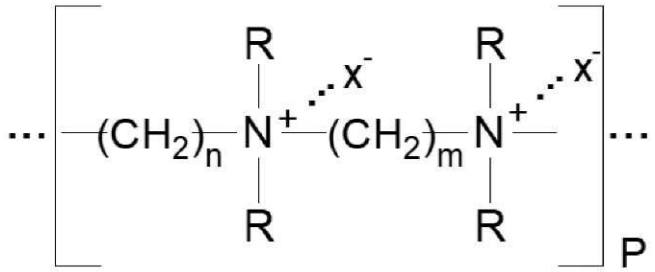
1. Soluble, biodegradable, or bioresorbable polymer carrier inert to the organism, capable of being excreted from the body in natural ways;
2. Type of bond between the polymer carrier and the active compound;

A - low-molecular biologically active compound;
B - high-molecular biologically active compound (biopolymer).

The intrinsic biological activity is attributed to low-molecular DS and inert polymers making long-term properties for artificial vessels, heart valves, and organs that are assigned to a separate group and are not considered in this paper. Also, results of studies of biopolymers, which are directly used in medicinal preparations in pure form as enzymes, hormones, heparin, etc. are not considered in this report. As noted above, the soluble neutral polymers were assigned to the BPs group with intrinsic activity. This group of polymers is the most studied and widely used in medical practice. This group includes blood and plasma substitutes for detoxification. They are designed to maintain an acceptable volume of circulating blood and the necessary value of osmotic pressure in time, which provides the restoration of blood loss. The polymer should be eliminated from the body without accumulation in vital organs. Considering the sufficient value of these polymers introduced into the body, it is necessary to control their toxicity. BPs of this type should be practically non-toxic and non-antigenic.

The most widely used anti-shock blood substitute since the middle of the last century is “clinical” dextran (polyglucin, macrodex, etc.). It was obtained by partial acidic hydrolysis of a high-molecular bactericidal dextran polysaccharide. Dextran is partially branched 1.6-a-polyglucosan, the side chains of which are attached to the main chain via 1.2-, 1.3-, 1.4-bonds [7]. In clinical practice, dextran-polyglucosan with Mw=50±10 thousand is used. The number of 1.6-a-bonds in the main chain is 93%, and the remaining 7% refers to the side 1.3- and 1.4-bonds. At the same time, there are no side 1.2-bonds in polyglucin. The therapeutic effect of dextran is determined by its colloid-osmotic properties and the viscosity of solutions and permeability through capillary vessels. It was established that dextran with Mw>200000 is toxic. Its fraction of Mw<50000 passes through the kidney, the smaller molecular mass is excreted faster. Also, dextran is subjected to enzymatic biodegradation in the body, which facilitates its excretion through the kidney. The finished product is glucose which is utilized by the body. 6-O-(2-hydroxyethyl) starch and poly-a, p-, (N-oxyethylaspartamide), as well as poly-N-(2-hydroxypropyl) methacrylamide were considered to be competitors of dextran as blood substitutes. Poly-N-(2-hydroxypropyl) methacrylamide as a chain polymer has not been subjected to biological degradation and is not widely used. Until recently, such blood

substitutes with detoxification properties, like low molecular weight carbochain polymers polyvinylpyrrolidone (hemodez and its corresponding foreign counterparts), polyvinyl alcohol (polydez), are subjected to biodegradation in the body, and dextran (reopolyglucin) with molecular mass 35000±5000 are able to form complexes both with low-molecular and high-molecular compounds in the body due to hydrogen bonds, hydrophobic effects, complexes formation, and other non-covalent interactions. The upper limit of the molecular mass of shown detoxicator should provide passing of the resulting complexes through the kidney. Because of the partial deposition of polyvinylpyrrolidone with a molecular mass of 70000-100000 in the body, its application in medicine is restricted. BPs with intrinsic activity include polycations with diverse biological activity mainly associated with their polyelectrolyte nature. It is known that proteins, nucleic acids, and a number of polysaccharides as natural biopolymers refer to as polyelectrolytes. When introducing mainly heterochain biosoluble polyesters into the body, in contrast to the charged functional groups, the cooperative interactions with the polycomplexes of the organism biopolymers with sufficient strength formed. Ionenes are the first polycations with studied biological activity and possible application in practical medicine as BPs. Ionenes are heterochain polymers containing quaternary nitrogen atoms in the polymer skeleton at the certain distances one from another having the following general structure



Where, n and m are the lengths of the hydrocarbon chain; R is the alkyl or aryl radical; X is the quaternary nitrogen counter-ion; P is the degree of polymerization. Ionic polymers showed high bactericidal activity, which depends on their structure. The proposed mechanism of bactericidal action of ionenes is explained by their adsorption on the bacterial cell walls. Ionene penetrated into the bacterial cell and forms a polyelectrolyte complex with DNA. The strength of this complex is directly dependent on the ion structure. It has been established that the ganglion-blocking activity of ionenes is directly dependent on the number of methylene groups. The direct interaction of ionenes to heparin has been proved by the formation of strong polyelectrolyte complexes without anticoagulant properties [8].

Based on this mechanism, a polymeric preparation polybrene neutralizing heparin in the bloodstream during surgery with the use of the artificial circulation apparatus has been developed. Ionens are not the only polymers that can neutralize heparin. Other polyionic polymers, such as poly (tert-amines) containing additional amide and carboxyl groups, have similar properties [9].

The natural aminopolysaccharide chitosan containing secondary amino groups can be conventionally referred to as the group of polymeric ionenes. Synthesized derivative of chitosan, sulfohitozan (sulfoparin) has anticoagulant properties that are not similarity to heparin that contains sulfate and sulfamine functional groups [10]. Biosoluble and biodegradable polyanions also belong to polymer forms with intrinsic biological activity. Nowadays, the biological activity of a number of polyanions has been established, in particular, their low anticancer, antiviral, immunomodulating, interferon-inducing, and other biological effects. However, weak biological activity does not allow them to be used as a pharmaceutical preparation.

The biological effects of polyanions are attributed to their polyanionic nature. In this connection, it can be assumed that the biological activity of exogenous polyanions is associated with competitive mechanisms and differ from polycation mechanisms related to the polycomplexes formation. A number of reviews [11-17] and original studies performed in recent years [18-20] have been devoted to biologically active polyanions. In this report, we made an attempt to determine the basic principles of polyanions biological activity and the prospects for their application in practice. It is known that sulfogroups-containing polyanions such as polyvinyl sulfonate, polyvinyl sulfate, dextran sulfate, sulfate chitosan, and other bio-soluble polymers are analogues of heparin, a polysaccharide sulfo-derivative.

They have shown anticoagulant, interferon-inducing, and anticancer activities [21]. The Hoechst Company produced the "Perhalen", which is the sodium salt of polyethylene sulfonate as an anticoagulant. It was the first synthetic polyelectrolyte applied in clinical practice, but its production has been stopped now because of high toxicity. Heterochain polyanions containing carboxyl groups, such as carboxymethylcellulose, carboxylcellulose, carboxymethyldextran, alginic acid, and their sodium salts are less toxic than polysulfated. Carbocyclic polycarboxylates such as polyacrylic acid and polymethacrylic acid and ethylene/maleic anhydride copolymer are relatively toxic and not subjected to biodegradation due to the polymer skeleton carbocetability. It has been established that the main criterion for the high biological activity of polyanions is the high density in the polymer skeleton of isotactic or syndiotactic carboxyl groups with molecular masses over ten thousand. The above polyanions are referred to carbochain polymers and not subjected to biodegradation in the organism. Biodegradable polyanions include carboxymethylcellulose and periodically oxidized modification of the unsubstituted hydroxyl groups at C_2 and C_3 positions, periodically oxidized amylose, starch, dextran, microcrystalline cellulose, and alginic acid.

These polymers have a high density of carboxyl groups and contain "weak acetal bonds". They exhibited weak antiviral and anticancer activity and low toxicity. Based on these polymers, a composition containing bound calcium ions in carboxyl groups of interest as a hemostatic agent was developed [22]. For a sufficiently long circulation of these polymers in the body, and their excretion by biodegradation, the optimal values of their MM should be in the range of 30-50 thousand. Based on the results of both heterochain and carbochain polyanions studies, it can be concluded that the actual task is to "separate" and establish optimal activity and toxicity for each type of polyanions. The toxicity of polyanions increases with MM>50000 when their anticancer activity persists even at MM<10000 (with these values of MM polyanions are low-toxic). It has also been shown that the antiviral activity of polyanions is relative to forcing at MM> 30000. The mechanism of antiviral action of polyanions is apparently associated with the activation of macrophages and inhibition of viral replication in the early stages of viral infection. From the above, the most promising clinical use of polyanions is the combination or chemical addition to various types of low-molecular antiviral drugs and antiviral vaccines in which polyanions can act as immunoadjuvants.

The immunoadjuvant activity of polyanions is closely related to their negative charge. For example, the immunoadjuvant activity of the polyanion dextran sulfate is high, while the original dextran is not active. The interferonogenic activity of polyanionic polymers is known. Interferon is a protein that provided the most rapid response to a viral infection and stimulates non-specific resistance of the organism. The interferon production is not always maintained in virus multiplication. Therefore, the induction of interferon by interferon inducers is one of the ways of viral infection control. Among the polymers, the synthetic polynucleotides poly (I) and poly (C) is the most active interferon inducers with a large therapeutic index. Similar activity is manifested by polyanions. Based on the results of our research, the polymeric interferon inducer based on polyanion carboxymethylcellulose and

antiviral polyphenol gossypol called “Kagocel” and “CelAgryp” was created in cooperation with the “Niarmedik Pharma” company, Russia.

It was introduced into medical practice as a preventive and curative remedy against influenza and acute respiratory viral infections [23-24]. The last group of BPs with intrinsic biological activity includes other polymers, and classification of which into groups in accordance with their chemical structure is difficult.

The mechanism of their biological activity is not fully established. One of the conditional groups of such polymers includes poly-N-tertiary amine oxides containing N-oxide functional groups in the skeleton or in the side groups. It was found that poly-2vinylpyridine-N-oxide possesses antifibrotic (antisilicase) action. In intravenous or inhalational administration, it inhibits the development of silicosis. The activity of this drug is determined by its MM=30-150000, the degree of tertiary group’s conversion to N-oxide, and the configuration of substituents in the main polymer chain. It may be suggested, that the antisilicic activity of the poly-N-oxide is associated with a cooperative interaction between a cell weak basic polymer and weak acid SiO_2. Other poly-N-oxides such as poly-N-allylpiperidine-N-oxide, poly-N-dimethylaminostyrene-N-oxide are similar to poly-2-vinylpiperidine-N-oxide. All poly-N-oxides are soluble in water, non-toxic, and have significant antifibrotic activity.

In addition to poly-N-oxides, a large number of biologically active polymers with intrinsic activity are known. So, aminopolysaccharide chitosan has a pronounced bactericidal activity. By chemical modification and regulation of deacetylation degree, a number of chitosan derivatives with different biological activities have been obtained [25-27]. Also known as poly-O-butyl alcohol-vinylin is used in medicine for the treatment of wounds, burns, frostbite, ulcers, gastritis, and colitis due to bacteriostatic, enveloping, and anti-inflammatory effects. As noted above, polymer forms of polyphenols with MM=6500-15000 have antiviral activity [28].

The molecular construction of medicinal polymers. In the molecular design of BPs the basic elements are more bioresoluble or biodegradable relatively inert carrier polymer, and low-molecular or high-molecular drugs. BPs of this type provided prolonged action of the drug substance, the selectivity of its action in respect to the internal organs, the positive effects due to a change in the hydrophilic-hydrophobic balance, the decrease of side effects, and the long-term preservation of the drug substance therapeutic concentration, a significant decrease of toxicity and an increasing of the specific action. The molecular design of polymeric drugs does not require the inclusion of drugs in the polymer structure, if a fast action of the drug is necessary, or if the drug is used in short-term treatment.

A positive effect achieved with the inclusion of a drug substance in the inert polymer structure is the prolonged circulation of the drug substance in the body due to a gradual release of the drug from the polymer carrier. At that, the therapeutic concentration of the drug in the body is maintained, and the frequency of its introduction into the body and the required dose is reduced.

Another important form of BPs is the form with the regulation of the hydrophilic-hydrophobic balance between DS and a carrier polymer. By changing the hydrophilic-hydrophobic balance, it becomes possible to transform the water-soluble state to insoluble by choice of polymeric carriers with high hydrophilicity. Using this principle, water-soluble polymeric derivatives of hydrophobic water-insoluble polyphenol gossypol were obtained by their chemical attachment to the hydrophilic polymer dialdehyde carboxymethylcellulose [29]. Analyzing the development of DS polymer forms and their use in medical practice, a number of limitations have been discovered, which include:

1. Adsorption of BPs in the gastrointestinal tract is not great, and the effect of this BPs in oral use is possible only after the release of the active principle from the polymer in the stomach or intestine;

2. Permeability of capillary barriers for polymers depending on its MM and chain-length distribution is different in various organs. Therefore, in parenteral injection, the BPs permeability via biomembrane determines the mismatching of the administration site and the action site.
3. Excretion of polymers is difficult in comparison to low-molecular drugs.
4. In particular, the permeability of polymers via the kidney biomembrane depends on the MM and polymer charge, the excretion (decomposition) of the polymers proceeds slowly.

Thus, it is preferable to use polymers as carriers that are metabolized with cleavage of the main chain to avoid their accumulation in the organs. In the case of undesirable consequences, such as overdose, allergy, etc. the rapid release of BPs from the body is difficult. In this view, a check of the BPs tolerability and a precise determination of the drug doses is necessary after re-application.

The drug polymers molecular design includes the following steps: selection of polymer carrier and assessment of its biological inertness, acute chronic toxicity, bio-solubility and biodegradability, and, if necessary, its functionalization; the type of bond between the PC and low molecular weight DS; choice of the type of low-molecular DS, and the need for prolongation of its action, possible ways of DS joining to PC; choice of type and the chemical bonds between polymer and BPs specific transport and selectivity. In BPs molecular designing, not all DS are included in the polymer structure. The creation of a polymeric form of BPs is relevant and important:

1. For low-molecular-weight DS used by frequent introduction into the body for a long time;
2. For DS with high toxicity;
3. For DS poorly soluble in water to obtain their water-soluble modifications;
4. To achieve selective delivery of BPs to “target organs” without their negative effect on internal organs;
5. To prolong the time of BPs action;
6. For BPs, non-storage-resistant forms of DS for the treatment of diseases requiring rapid exposure to their target organs, for DS of a single administration.

The polymer carrier chosen as a matrix-based for new BPs creation must be non-toxic, organotypic, and readily susceptible to bioremediation and biodegradation since it determines the BPs physic-chemical and biological properties. The polymer carrier used in BPs creation should meet the following requirements:

1. Must be biosoluble and biodegradable;
2. MM and chain-length distribution of the polymer carrier determine the duration of its circulation in the bloodstream. If it is necessary to introduce BPs into the cells by endocytosis and, at the same time, to excrete them by the kidney, the MM of the polymer carrier must be sufficiently low. This contradiction can be solved by choosing biodegradable PC;
3. The polymer carrier must contain reactive functional groups or be readily functionalized. Between the functional groups of polymer carrier and low molecular weight DS the reactions must proceed easily and unambiguously;
4. The polymer carrier must be organized, non-toxic, compatible with blood, and non-antigenic.

A perfect polymer carrier that completely meets all of the above requirements is not available. The main and widely used heterochain polymer carriers in the development of polymer forms of DS are dextran, starch, carboxymethyl-, methyl-hydroxyethylcellulose, alginic acid, chitosan, pectin, gelatin, serum albumin, globulins, antibodies, polyaminoacids;

carriers - polyvinylpyrrolidone, polyvinyl alcohol, polyethylene polyamine, substituted acrylates and acrylamides, homo- and copolymers of acrylic and methacrylic acid, etc. In the molecular design of polymer form drugs, the type of chemical bond between the PC and the low molecular weight compound is of great importance. The nature of the relationship between DS and the polymer carrier is the determining factor in a target BPs application. Depending on the mechanism of its localization in the body, the chemical bond between BPs and polymer-carriers is important since hydrolytic stability determines the mechanism of the BPs biological activity manifestation Depending on the direction and localization of BPs, they can be divided into three groups:

1. BPs acting outside of the cell. This type of BPs can include enzyme inhibitors, anticoagulants, neutralizers, antibiotics acting on extracellular bacteria, parasites, etc. DS should separate gradually from the abovementioned BPs, preserving the original structure, long maintaining the minimum therapeutic concentration in the blood, intercellular and other body fluids. For prolonged circulation in the bloodstream, the BPs must have a sufficiently high MM, and, at the same time, its endocytosis should be minimal. The rate of DS degradation from the polymer carrier in the bloodstream or other body fluid should be such that the main part of the DS can be decomposed, but its concentration in the body should be commensurable with the rate of DS excretion or metabolism. Otherwise, toxic effects and cumulation of associated BPs occur. These DS adverse effects are related to the nature and type of bonds between the polymer carrier and DS and can be removed by the choice of chemical bond type. Thus, by selecting the appropriate type of connection between the PC and BPs, its steric and charges environment, the rate of DS elimination from the polymer carrier, and, correspondingly, its activity and duration of action can be controlled.
2. BPs acting on the cell surface. This type of BPs refers to the activity on the target cell`s surface membrane. In this case, there is no need for the penetration of BPs into the cell. For these BPs types, it is desirable to preserve their activity in a polymeric form, that is, their activity on the cell surface is preserved without hydrolytic cleavage of DS and BPs, and should directly influence the cell receptors. Other variants of BPs interaction on the cell surface include DS bound by cell-specific polymers. This type of polymer is not active on the cell surface, and DS is destroyed on the cell surface by enzymes or short-lived enzymes isolated from the cell. This mechanism of the BPs effect on the cell is not investigated fully.
3. BPs acting inside the cell. This group includes BPs that can penetrate into the cell via the cell membrane, such as antibacterial and antitumor compounds. The mechanisms of low-molecular DS and BPs penetration are significantly different.

In particular, if DS is penetrated into the cell by passive diffusion or active transport, BPs are penetrated by endocytosis, that`s why their therapeutic effects differ. The endocytosis mechanism of BPs in the cell has a number of advantages, in contrast to the penetration of low-molecular BPs into the cell. By endocytosis of BPs, the DS could penetrate via the cell membrane. The greatest effect is achieved in the penetration of DSs that affect the lysosomes. In this case, the lysosomal enzymes destroy BPs in DS, and the polymer carrier is also subjected to destruction.

The type of connection between the polymer carrier and DS, and BPs structure determines the way of its penetration into the cell, localizes its site of action, and the mechanism of DS exposure in the body. The binding of BPs to the PC can be achieved by various types of chemical bonds, such as covalent, ionic, coordination, cooperative, etc. Among these bonds, covalent and ionic bonds play the largest role. Ionic binding of BPs, for example, proteins to PC, polyelectrolyte complexes, can result in the gradual release of the active principle (protein) from the polymer carrier gradually, since DS is in loops of “defects”

and released from the PC during the re-arrangement of complexes in the body. In most cases, when the low-molecular DS is bound by an ionic bond to polyelectrolyte polymers carrier, the bond has not had enough strength, and BPs is rapidly destroyed when the pH and ionic strength of the medium change. The most suitable types of connection between DS and the polymer carrier are covalent bonds of various types. On stability, covalent bonds can be divided into four types:

1. Labile bonds gradually hydrolyzed without the participation of enzymes when pH and ionic strength in the body changed;
2. Relatively labile bonds that are susceptible to slow hydrolysis without the participation of enzymes, although they quickly break down depending on steric and charging effects;
3. Relatively stable bonds, which are hydrolyzed only enzymatically at a noticeable rate;
4. Stable connections, which are hydrolyzed neither in vitro or in vivo in most cases. Such bonds include amine, azo, and ether bonds. They can disintegrate by other mechanisms, under the influence of neighboring groups, but not by a hydrolytic mechanism. The kinetic parameters of DS and BPs release are variable, the process is complex and incomplete.

The chemical attachment of BPs to the carrier polymer can be carried out directly by incorporating the reactive groups in BPs and the polymer carrier. Each of these approaches has its advantages and disadvantages, and the choice of strategy for BPs creation depends on the specific requirements for BPs. Specific BPs transportation to organs is the main factor determining their selectivity. There are three levels of selectivity of BPs acting on the surface or inside cells [30, 31]. At the first level, the PC has a negative effect on non-target cells upon BPs admission into the body.

At the second, higher level, the concentration of BPs around the “target cell” is quite high in comparison to other cells; in other words, BPs concentration around non-target cells is lower. The third-highest level of selectivity is the MP solely action on the target organ cells. For BPs acting on the cell surface, the first two levels of selectivity are acceptable, which result from the hydrophilic-lipophilic effect of BPs when it is distributed between plasma, lymph, and intercellular fluid. In this case, due to the low permeability of BPs via capillary and other barriers, the

BPs attached to the polymers are converted from general to local or limited-acting substances. In the case of BPs acting inside the cell, their selectivity is achieved, in addition to the first two levels, also due to changing the way of their penetration inside the cell. Cells that are capable of enhanced endocytosis absorb more DS than other cells. For example, polyanions are susceptible to increased endocytosis and attract great interest as a good carrier for DS of intracellular action that readily achieved the second level of selectivity.

The third level of selectivity is achieved when BPs is recognized by certain cell types (target cells) due to specific effects. In this case, the BPs remain on the cell surface membrane or penetrate into the cell by endocytosis. BPs ability to penetrate into the cell is determined by the specific distribution of the PC on the targeted cell surface, like in affinity chromatography, but in the case of cells, the process proceeds in vivo. Polymer carriers with cationic functional groups are mainly absorbed on the cell surface, and their selectivity is determined by the magnitude of the cell surface’s negative charge. Taking this into account in the design of BPs, it is necessary to consider also the chemical and immunological properties of target organs for the selection of necessary ligands for attachment to the polymer carrier and the necessary DS.

Based on the foregoing, it can be concluded that the problem of BPs specificity and penetration into the target cells has not been fully studied, and there is only fragmentary

information on the penetration of BPs into tumor target cells. All the above types of BPs belong to water-soluble compounds.

However, DS can also be attached to water-insoluble carriers that are capable to interact with cell surface receptors. In this case, BPs are attached to water-insoluble, finely dispersed, biocompatible polymer-carriers. Such systems are of interest for diagnostic and research purposes. For such insoluble polymer-carrier, the terms microparticle, microsphere, and nanoparticle are often used. It is known that some water-insoluble heterochain PC, to which BPs are attached, can be decomposed under mild conditions with the release of water-insoluble fragments.

In particular, the insoluble sorbent of Sephadex, to which the DS is attached, can swell unlimitedly due to gradual degradation and become soluble. The polymer carrier with attached DS can be attributed to this BPs group; in the body, they swell and gradually degrade with the transition of fragments into a soluble state.

Another type of microparticles includes water-insoluble DS carriers or microparticles that can penetrate into cells in an undissolved state or sorb on their surface. These BPs include compounds with particle sizes in the nanometer range with a relatively narrow particle size distribution.

Two types of compounds belong to these biologically active BPs:

1. Nanosized PC containing DS as spherical nanocapsules or nanoparticles;
2. Nanopolymer systems or nanostructured polymers containing DS nanoparticles, including metal nanoparticles, which possess biological activity.

Above BPs types, selectivity can be achieved by incorporating the ferromagnetic nanoparticles into their structure, which allows the in vivo control of nanoparticles by means of a magnetic field. The creation of BPs with micro-, and nanoscale particles helps to increase the level of DS transport in target organs. This effect is achieved by selective adsorption or absorption of nanoparticles in a certain type of cells whose surfaces have a biospecific affinity for the surface of polymeric nanoparticles, which have an increased tendency to endocytosis.

In general, this type of BPs must contain three types of components to perform its functions:

– BPs affecting selectively to the determined cells;
– Agents recognize only certain cells due to biospecific effects;
– Factors of penetration ensure the intake of DS into the cells.

Taking into account the above, we synthesized a number of biologically active BPs with specific properties. Based on the water-soluble functionalized PC, an antiviral polymer preparation with interferon-inducing properties has been synthesized with hydrophobic water-insoluble natural polyphenol gossypol as BPs. Due to changes in the hydrophilic-lipophilic properties during the addition of gossypol to the PC, the resulting BPs are soluble in water. The resulting BPs had direct antiviral and interferon-inducing activity due to the attached gossypol and polyanionic structure of the PC. This BPs drug was introduced into medical practice under the name “CelAgryp” in Uzbekistan as a preventive and curative remedy for viral influenza and acute viral respiratory infection [32].

Given the high antiviral activity of these drugs, we developed polymer-polymer nanocomplexes based on the polymeric form of “CelAgryp” substance and polymer substrate polyanionic sodium-carboxymethylcellulose. By varying the polymer-polymer compositions synthesis conditions and formation of films on their basis, transparent bio-soluble and biodegradable antiviral films were obtained, and the gelled polymeric form of “CelAgryp” substance in the matrix was evenly distributed with a particle size of 20-35 nm. The resulting biodegradable films showed high antiviral activity against ophthalmoherpes. Thus, for the first time, the antiviral biodegradable nanostructured polymer form eye drug film of “GlazAvir” has been synthesized for the prevention and treatment of viral eye diseases.

Another area of new BPs is the formation of metal nanoparticles with bactericidal and bacteriostatic properties in the structure of a polyanionic carrier polymer, sodium-carboxymethylcellulose (Na-CMC). As a biologically active metal-silver is chosen for bactericidal and bacteriostatic properties. Synthesis of silver nanoparticles in the polymer-carrier structure was carried out by photo-irradiation of Ag^0CMC solutions in excess of Ag^+. By varying the ratio of the reactant components, their concentrations, and reaction parameters, the solutions, hydrogels, film, and BPs powders containing spherical and rod-like silver nanoparticles with sizes of 5-25 nm were obtained. The stabilization of silver nanoparticles in the structure of the polymer matrix is explained by the enveloping of silver particles by polyanion macromolecules capable of interrelation. The obtained BPs has shown high biological activity against a wide range of bacteria and fungi [33-38].

Conclusion

Based on the above, it can be concluded that the creation of new BPs relates to the developing field of chemistry, biology, and pharmacology of high-molecular compounds. The basic principles for the creation of new BPs, considered in this paper, may be considered in the molecular design of polymer forms of biologically active compounds. Advances in BPs synthesis are apparently related to the experimental elucidation of BPs action mechanisms and the choice of purposeful ways and approaches to their synthesis.

Advances in new BPs creation with a targeted effect on the body will be related to the correct and scientifically justified choice of carrier polymers, DS, the establishment of BPs fine molecular structure and the effect of their biological activity, the realization of targeted BPs transport to target organs, and mechanisms of BPs and DS penetration into the cell.

It the creation of new BPs, a large value is assigned to the covalent bond formation between BPs and carrier polymer. In contrast to DS, for BPs, the concept of structure is much broader. In addition to DS and carrier polymer structure, the compositional and structural inhomogeneity plays an important role; since the interactions of BPs with macromolecules have a cooperative nature, the polymer effect manifests itself, while the structure regularity for achieving the resulting polycomplexes stability between BPs and the organism is the determining factor. Structural heterogeneity of BPs can often lead to various biological effects, including the manifestation of toxicity.

Stereochemistry and chain-length distribution of the polymer is playing an important role in the manifestation of BPs biological activity. For polyanions, it has been established that biological activity and toxicity are the functions of chain-length distribution.

Taking the above in mind it is necessary to identify the narrowest fractions of chain-length distribution and study their activity in BPs development. Thus, it can be concluded that BPs and the practical possibilities of their creation are unique in many cases and can be not achieved by low-molecular DS use.

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References

[1] Shtilman M. I., Podkorytova A. V., Nemtsev S. V., Kryazhev V. N. Technology of polymers for medical and biological purposes. *Polymers of Natural Origin: A Study Guide*// 3rd edition, Publishing House "Laboratory of Knowledge", 331 p. **(2020)**

[2] Vasiliev A.E. Medicinal polymers. *The results of science and technology*, V. 16. 119 p. **(1981)**

[3] Shtilman M.I. Polymers for medical and biological purposes. Moscow: Academic Book; 400 p. **(2006)**

[4] Milusheva R.Yu., Inoyatova F.H., Batyrbekov A.A., Rashidova S.Sh. Hepatoprotective, anticoagulant and immuno-stimulating properties of chitosan *Bombyx Mori* derivatives, *Advances in chitin science*, XI, pp. 180-184. **(2011)**

[5] Yunusov Kh.E., Rashidova S.Sh., Sarymsakov AA, Atakhanov A.A. Medico-biological polymers and prospects for their creation. *Pharmaceutical Journal*. Tashkent, No. 3. pp. 27-35. **(2011)**

[6] Kasymova G.Z., Sabirova R.A., Milusheva R.Yu. The effect of different forms of chitosan on the redox processes in the liver in the metabolic syndrome "*Physician-graduate*", No. 3, i. 3(52), pp. 432-437. **(2012)**

[7] Sidebotham R.L. Adv. *Carb. Chem., V.* 30, pp. 371-444. **(1974)**

[8] Rembaum A. Applied *Polymer Symp.*, No. 22, pp. 229-317. **(1973)**

[9] Ferutte P. IeFarmaco, Ed. *Sci.*, 32, No. 3, pp. 220-236. **(1977)**

[10] Rashidova S.Sh., Milusheva R.Yu., Advances in Chitin Science, 10th International Conference of the European Chitin Society, Volume X1 St. Petersburg, pp. 230-235. **(2011)**

[11] Regelson W. In: Water-Soluble Polymers. Ed. N. M. Bikales. N.Y. L., *"Plenum Press"*, pp. 161-177. **(1973)**

[12] Butler G.B. J. Polymer Sci., Polymer Symp. No. 50, pp. 160-180. **(1975)**

[13] Regelson W., Morahan P., Kaplan A. In: Polyelectrolytes and their applications. Eds. A. Rembaum, E. Sefeny., pp. 131-144. **(1975)**

[14] Breslov, D. S. Pure *Applied Chem., V*. 46, No. 2-4, pp. 103-113. **(1976)**

[15] Ottenbrite R. M., Regelson W., Kaplan A., Carchman R., Morahan P., Munson A. In: Polymeric Drugs. Eds. L. G. Donaruma, O. Vogl. N. Y. San Francisco - L., *Acad. Press*, pp. 263-303. **(1978)**

[16] Levy H. B. In: Polymeric Drugs, Eds. *Academic press*, New York. N.Y., pp. 305-329. **(1978)**

[17] Regelson W. J. Polymer Sci., *Polymer Symp.*, No. 66, pp. 483-538. **(1979)**

[18] Sarymsakov A.A., Yunusov Kh.E., Atakhanov A.A., Rashidova S.Sh., Medico-biological polymers and prospects of their creation. *Pharmaceutical Journal*, pp. 27-35. **(2011)**

[19] Yunusov Kh.E., Atakhanov A.A., Ashurov N.A., Sarymsakov A.A., Rashidova S.Sh. Physicochemical studies of cotton cellulose and its derivatives containing silver nanoparticles, *Chemistry of Natural Compounds: V*. 47, I. 3, pp. 415-418. **(2011)**

[20] Vokhidova N.R., Sattarov M.E., Kareva N.D., and Rashidova S.Sh. Fungicide Features of the Nanosystems of Silkworm (Bombyxmori) Chitosan with Copper Ions *// Microbiology, V.* 83, No. 6, pp. 751-753. **(2014)**

[21] Regelson W., Holland J. F. "*Nature*", V. 181, No. 4601, pp. 46-47. **(1958)**

[22] Kholturaev B.Dj., Atakhanov A.A., Sarymsakov A.A., Obtaining polymer-containing blood-stopping drugs and their physico-chemical properties, "Development prospects of chemistry and technology of natural and synthetic polymers" Proceedings of the Republican Scientific and Technical conference, Tashkent-2019, pp. 60-61. **(2019)**

[23] Sarymsakov A.A., Rashidova S.Sh., Azizova M.A. Methods for producing a copolymer having properties against chronic respiratory viral infections based on gossypol and carboxomethyl cellulose, *IAP* 04811 Tashkent, 17.12.2013. **(2013)**

[24] Azizova M.A., Sarymsakov A.A., Rashidova S.Sh. Synthesis and biomedical testing of polymeric forms of an interferon inducer with antiviral activity, "Development prospects of chemistry and technology of natural and synthetic polymers" Proceedings of the Republican Scientific and Technical Conference, Tashkent-2019, pp.10-11. **(2019)**

[25] Kudyshkin V.O., Futoryanskaya AM, Milusheva R.Yu., Kareva N.D., Rashidova S.Sh. Synthesized graft copolymers of chitosan Bombyxmori and N-vinylcaprolactam. *Doklad Akademii Nauk RUz*, No.2, pp. 60-63. **(2010)**

[26] Rashidova S.Sh., Milusheva R.Yu., Yugay S.M. Nanomaterials Based on Chitosan of Bombyx mori, *Advances in chitin science*, XI. pp. 230-235. **(2011)**

[27] Milusheva R.Yu., Song W., Rashidova S.Sh. Bionanocomposites Based on Chitosan of Bombyx Mori and Sepiolite Pangel S9, *Advances in chitin science*, XI, pp. 132-133. **(2011)**

[28] Sarymsakov A.A., Li Yu.B., Rashidova S.Sh. Eye medicinal films for the treatment of viral diseases of the eye. *Korean Newsletter "Tinbo*", pp. 58-64. **(2014)**

[29] Ershov F.I., Sarymsakov A.A., Nesterenko V.G., Rashidova S.Sh. and etc. *Patent of the Russian Federation No. 2270708*, **(2003)**

[30] Ringsdorf H. In: “Polymeric Drug Delivery Systems”. Ed by Kostelnik B. N. Y., Gordon Breach, 197 p. **(1978)**

[31] Trouet A. In: Polymeric Drug Delivery Systems. Ed by Kostelnik N. Y., Gordon Breach, pp. 157-173. **(2013)**

[32] Sarymsakov A.A., Rashidova S.Sh., Aripova T.U. New in the prevention and treatment of influenza and ARVI, Tashkent-2010, pp. 110-112. **(2010)**

[33] Vokhidova N.R., Nurgaliyev I.N., Ashurov N.S., Yugay S.M., Rashidova S.Sh. Obtaining and stabilization mechanisms of cobalt nanoparticles based on chitosan bombyx mori 2015 CIS-Korea conference on science and technology, pp. 270-273. **(2015)**

[34] Yunusova Kh.E., Atakhanova A.A., Ashurova N.A., Sarymsakova A.A., Rashidova S.Sh. Physico-chemical studies of cotton cellulose derivatives containing silver nanoparticles. *Journal of Chemistry of Natural Compounds*, Uzbekistan-2011, No. 3. pp. 370-373. **(2011)**

[35] Vokhidova N.R., Pirniyazov K.K., Rashidova S.Sh. Formation and stabilization of metal nanoparticles in polymer matrices. Review article. Proceedings of the Institute of Chemistry and Polymer Physics of the Academy of Sciences of Uzbekistan. Tashkent,. pp. 128-145. **(2011)**

[36] Yunusov Kh.E., Atakhanov A.A., Sarymsakov A.A., Rashidova S.Sh., Lobanova K.V., Tashpulatov Zh.Zh. Nanoparticles of silver, formed on polymer matrices and their bactericidal properties. *Pharmaceutical Journal*, 1, pp. 55-59. **(2010)**

[37] Oksengendler B.L., Turaeva N., Maksimov S.E., Dzhurabekova F.G. Peculiarities of the radiation defect formation in nanocrystals embedded in a solid matrix, *ZhETF*, V. 138, I. 1(7), pp. 1-6. **(2010)**

[38] Mailoa, M. N., Mahendradatta, M., Laga, A., & Djide, N. Tannin extract of guava leaves (Psidium guajava L) variation with concentration organic solvents. *International Journal of Scientific & Technology Research, V.*2(9), pp. 106-110. **(2013)**