# Features In Creating Polymer Forms Of Drugs

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**Abstract**: In this article, the results of medicinal compounds polymeric forms classification and principles of their development are discussing. The basic requirements for carrier polymers and polymers with own biological activity are developed. The main differences in creating low-molecular drugs, their polymer forms and polymers with their own biological activity. Polications assigned to the group of ionenes were isolated and examined separately. Heterochain polymers containing quaternary nitrogen atoms at certain distances from each other are classified as ionenes. Ionenes have high bactericidal activity depending on the structure, which is explained by their adsorption to the bacterial cell walls. The formation of polyelectrolyte complexes with DNA is possible with the penetration of ionenes into bacteria cells. Polyanions are also referred to polymer forms of medical substances. Biological effect of exogenous polyanions is explained by competitive mechanisms rather than with the formation of polycomplexes. 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. The scientific work also examined 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. Were established limitations for carrier polymers in molecular construction and creation of polymer forms of drugs. A list of classes of drugs, for which the creation of their dosage forms is relevant, was also defined. Based on the results of the research, it was concluded that drug polymers and practical possibilities of their creation are in many cases unique and cannot be achieved with the use of low molecular weight drugs.

**Index Terms**: polymer, drug, biodegradations, cellulose, carboxymethylcellulose, nanostructured, biological activity.

## 1. INTRODUCTION

Development of polymer science and pharmaceutical industry are of particular importance for the creation of new types of natural and synthetic polymer forms of original preparations and medical products. Past period, the development of nanotechnologies provided the large-scale scientific researches in this field. Analysis of chemistry and physical chemistry development, including nanochemistry and nanotechnology, in creation of original pharmaceutical products shows that polymeric nanostructured biologically active compounds have a number of advantages, unlike to 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 principle - 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 the principles that determine 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 physic-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 medicinal polymers (MP) with “intrinsic” biological activity is related to diversified and also low molecular weight DS. MP with “intrinsic” biological activity can be divided into four large groups [2]. DS polymeric forms includes polymers naturally occur in the organism, or “carrier polymers” (CP), and low-molecular or high-molecular DS. Such polymers can be conditionally attributed to the group of “inoculate” type polymers, as in CP overwhelming state the low- and high-molecular medical compounds (active principles) are chemically attached (grafted) to CP 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 MPs varies due to the basic principles of carrier polymer molecular design and low or high molecular weight of DS.

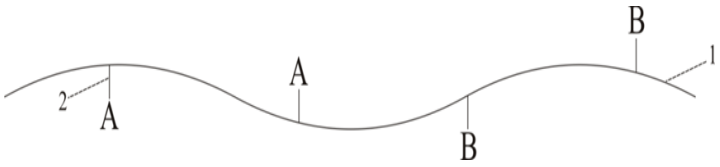


***Fig 1.*** *Polymeric forms of drug substances with intrinsic activity [3-6]*

1. Soluble, biodegradable, or bioresorbable carrier polymer inert to the organism, capable of being excreted from the body by natural ways;
2. Type of bond between the carrier polymer 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 a long-life polymeric products for artificial vessels, heart valves, and organs that are


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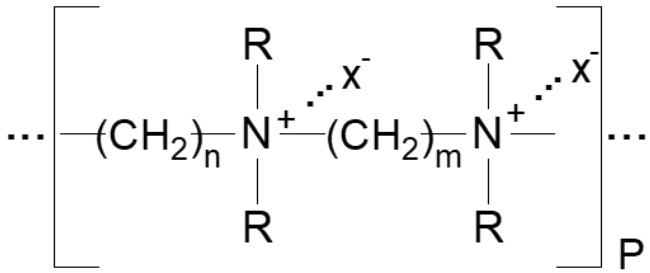
assigned to a separate group and are not considered in this paper. Also, results of studies of biopolymers, which are directly used in medicinal preparations in pure form as enzymes, hormones, heparin, etc. are not considered in this report.As noted above, the soluble neutral polymers were assigned to the MP 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 a sufficient value of these polymers introduced into the body, it is necessary to control their toxicity. MPs of this type should be practically non-toxic and non-antigenic.

## 2 METHODS OF RESEARCH

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-α-polyglucosan, the side chains of which are attached to the main chain via 1,2-, 1,3- and 1,4-bonds [7]. In clinical practice, dextran-polyglucosan with Mw = 50±10 thousand is used. The number of 1,6-α-bonds in the main chain is 93%, 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 finish product is glucose which is utilized by the body. 6-O-(2-hydroxyethyl) starch and poly-α, β-(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 molecular mass of 70000-100000 in the body, its application in medicine is restricted. MS polymeric forms 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 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 MP. 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 length of the hydrocarbon chain;
R- alkyl or aryl radical;
X- quaternary nitrogen counter-ion;
P - 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 forms polyelectrolyte complex with DNA. 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 formation of strong polyelectrolyte complexes without anticoagulant properties [8]. Basing 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 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 MS polymer forms with intrinsic biological activity. Nowadays, 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 carboxymethyl cellulose, carboxyl cellulose, carboxymethyl dextran, alginic acid, and their sodium salts are less toxic than polysulfates. Carbocchic polycarboxylates such as polyacrylic acid and polymethacrylic acid, 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 high biological activity of polyanions is the high density in the polymer skeleton of isotactic or syndiotactic carboxyl groups with molecular masses over a 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 C2 and C3 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 a low toxicity. Based on these polymers, a composition containing bound calcium ion 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 activation of macrophages and inhibition of viral replication on 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. Interferonogenic activity of polyanionic polymers is known. Interferon is a protein provided the most rapid response to a viral infection and stimulating non-specific resistance of the organism. The interferon production not always maintains in virus multiplication. Therefore, the induction of interferon by interferon inducers is one of the ways for viral infections control. Among the polymers, the synthetic polynucleotides poly (I) and poly (C) are 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 carboxymethyl cellulose and an antiviral polyphenol gossipol called “Kagocel” and “CelAgryp” was created in cooperation with the “Niarmedik Pharma” company. 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 polymeric MS with intrinsic biological activity includes other polymers, 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-2 vinylpyridine-N-oxide possesses antifibrotic (antisilicase) action. In intravenous or inhalational administration, it inhibits the development of silicosis. Activity of this drug is determined by its MM = 30-150000, the degree of tertiary groups conversion to N-oxide, and the configuration of substituents in the main polymer chain. It may be suggest, that the antisilicic activity of the poly-N-oxide is associated to a cooperative interaction between a cell weak basic polymer and weak acid SiO2. 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 activity have been obtained [25-27]. Also known 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]. Molecular construction of medicinal polymers. In the molecular design of MP the basic elements are more bioresoluble or biodegradable relatively inert carrier polymer, and low-molecular or high-molecular drugs. MPs 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, therapeutic concentration of the drug in the body is maintained, and frequency of its introduction into the body and a required dose is reduced. Another important form of MP is the form with 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 a hydrophobic water-insoluble polyphenol gossypol were obtained by its chemical attachment to the hydrophilic polymer dialdehyde carboxymethylcellulose [29]. Analyzing the development of DS polymer forms of and their use in medical practice, a number of limitations have been discovered, which include:

1. Adsorption of MP in the gastrointestinal tract is not great, and effect of this LP 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 MP permeability via biomembrane determines the mismatching of the administration site and the action site.
3. Excretion of polymers is difficult in compare 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 that avoids their accumulation in the organs and tissues. 4. In the case of undesirable consequences, such as overdose, allergy, etc. the rapid release of LPs from the body is difficult. In this view, a check of the MP 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 a carrier polymer and assessment of its biological inertness, acute chronic toxicity, bio-solubility and biodegradability, and, if necessary, its functionalization; the type of bond between the carrier polymer 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 carrier polymers; choice of type and the chemical bonds between polymer and MP; MP specific transport and selectivity. In MP molecular designing, not all DS are included in the polymer structure. Creation of a polymeric form of MP 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. 4.To achieve selective delivery of MP to “target organs” without their negative effect on internal organs;
5. To prolong the time of MP action;
6. For MPs, 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 carrier polymer chosen as a matrix-base for new MP creation must be non-toxic, organotropic and readily susceptible to bioremediation and biodegradation, since it determines the MP physic-chemical and biological properties.

The carrier polymer used in MP creation should meet the following requirements:

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

Perfect carrier polymer 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 drug polymer forms, the type of chemical bond between the carrier polymer and the low molecular weight compound is of great importance. The nature of the relationship between DS and the carrier polymer is the determining factor in a target MP application. Depending on the mechanism of its localization in the body, the chemical bond between MP and a carrier polymer is important since hydrolytic stability determines the mechanism of the MP biological activity manifestation Depending on the direction and localization of MP, they can be divided into three groups:

1. MP acting outside of the cell. This type of MP can include enzyme inhibitors, anticoagulants and their neutralizers, antibiotics acting on extracellular bacteria, parasites, etc. DS should separate gradually from the abovementioned MP, 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 MP must have a sufficiently high MW, and, at the same time, its endocytosis should be minimal. The rate of DS degradation from the carrier polymer in 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 MP is occur. These DS adverse effects related to the nature and type of bonds between the carrier polymer and DS, and can be remove by the choice of chemical bond type. Thus, by selecting the appropriate type of connection between the carrier polymer and LB, it’s steric and charge environment, the rate of DS elimination from the carrier polymer, and, correspondingly, its activity and duration of action can be controlled. 2. MP acting on the cell surface. This type of MP refers to the activity on the target cell’s surface membrane. In this case, there is no need for the penetration of MP into the cell. For these MP types, it is desirable to preserve their activity in a polymeric form, that is, their activity on the cell surface preserved without hydrolytic cleavage of DS and MP, and should directly influence on the cell receptors. Other variants of MP 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 destroying on the cell surface by enzymes or short-lived enzymes isolated from the cell. This mechanism of MP effect on the cell is not investigate fully. 3. MP acting inside the cell. This group includes MP that can penetrate into the cell via the cell membrane, such as antibacterial and antitumor compounds. The mechanisms of low-molecular DS and MP penetration are significantly different. In particular, if DS is penetrated into the cell by passive diffusion or active transport, MP is penetrated by

endocytosis, that's why their therapeutic effects differ. The endocytosis mechanism of MP in the cell has a number of advantages, in contrast to the penetration of low-molecular LV into the cell. By endocytosis of MP the DC could penetrate via cell membrane. The greatest effect is achieved in penetration of DSs that affect on the lysosomes. In this case, the lysosomal enzymes destroy MP in DS, and the carrier polymer also subjected to destruction. The type of connection between the carrier polymer and DS, and MP 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 MP to the carrier polymer can be achieve by various types of chemical bonds, such as covalent, ionic, coordination, cooperative etc. Among these bonds, covalent and ionic bonds play a largest role. Ionic binding of polymeric MPs, for example, proteins to carrier polymers, i.e., polyelectrolyte complexes, can result in the gradual release of the active principle (protein) from the carrier polymer gradually, since DS is in loops of "defects" and released from the carrier polymer during the re-arrangement of complexes in the body. In the most cases, when the low-molecular DS is bound by ionic bond to polyelectrolyte carrier polymers, the bond has not enough strength, and MP is rapidly destroyed when pH and ionic strength of the medium change. The most suitable types of connection between DS and the carrier polymer 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 is 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 not hydrolyze neither in vitro nor in vivo in the most cases. Such bonds include amine, azo, and ether bonds. They can be disintegrate by other mechanisms, under the influence of neighboring groups, but not by a hydrolytic mechanism. The kinetic parameters of DS and MP release are variable, the process is complex and incomplete.

The chemical attachment of MP to the carrier polymer can be carried out directly and by incorporating the reactive groups in MP and the carrier polymer. Each of these approaches has its advantages and disadvantages, and the choice of strategy for MPs creation depends on the specific requirements for MP. Specific MP transportation to organs is the main factor determining their selectivity. There are three levels of selectivity of MP acting on the surface or inside cells [30, 31]. At the first level, the carrier polymer has a negative effect on non-target cells upon MP admission into the body. At the second, higher level, the concentration of MP around the "target cell" is quite high in compare to other cells; in other words, MP concentration around non-target cells is lower. The third highest level of selectivity is the MP solely action on the target organ cells. For MP acting on cell surface, the first two levels of selectivity are acceptable, that result from the hydrophilic-lipophilic effect of MP when it distributed between plasma, lymph and intercellular fluid. In this case, due to the low permeability of MP via capillary and other barriers, the MPs attached to the polymers are converted from general to local or limited-acting substances. In the case of MP acting inside the cell, their selectivity achieved, in addition to the first two levels, also due to changing the way of their penetration inside the cell. Cells that are capable to 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 second level of selectivity. The third level of selectivity is achieved when MP is recognized by certain cell types (target cells) due to specific effects. In this case, the MP remains on the cell surface membrane or penetrates into the cell by endocytosis. MP ability to penetrate into the cell is determined by the specific distribution of the carrier polymer on the targeted cell surface, like in affinity chromatography, but in the case of cells the process proceeds in vivo. Carrier polymers with cationic functional groups are mainly absorbed on the cell surface, and their selectivity is determined by the magnitude of the cell surface negative charge. Taking this into account in the design of MP, it is necessary to consider also the chemical and immunological properties of target organs for the selection of necessary ligands for attachment to the carrier polymer and the necessary DS. Based on the foregoing, it can be concluded that the problem of MP specificity and penetration into the target cells has not been fully studied, and there are only fragmentary information on the penetration of MP into tumor target cells. All the above types of MP 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, MP attached to water-insoluble, finely dispersed, biocompatible carrier polymers. Such systems are of interest for diagnostic and research purposes. For such insoluble carrier polymers, the terms microparticle, microsphere, nanoparticle is often used. It is known that some water-insoluble heterochain polymer carriers, to which MP are attached, can be decomposed under mild conditions with the release of water-insoluble fragments. In particular, the insoluble sorbent sephadex, to which the DS is attached, can swell unlimitedly due to gradual degradation and become soluble. The carrier polymers with attached DS can be attributed to this MP 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 can penetrate into cells in undissolved state, or sorb on their surface. These MP 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 MP:**

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

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

endocytosis.

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

- MP affecting selectively to the determined cells;
- Agents recognizing only certain cells due to biospecific effects;
- Factors of penetration ensuring the intake of DS into the cells.

Taking into account the above, we synthesized a number of biologically active MP with specific properties. Based on the water-soluble functionalized carrier polymer, an antiviral polymer preparation with interferon-inducing properties has been synthesized with hydrophobic water-insoluble natural polyphenol gossypol as MP. Due to changes in the hydrophilic-lipophilic properties during the addition of gossypol to the carrier polymer, the resulting MP is soluble in water. The resulting MP had direct antiviral and interferon-inducing activity due to the attached gossypol and polyanionic structure of the carrier polymer. This MP 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 Na-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, the gelled polymeric form of “CelAgryp” substance in the matrix was evenly distributed with a particle sizes of 20-35 nm. The resulting biodegradable films showed high antiviral activity against ophthalmoherpes. Thus, for the first time, antiviral bioresoluble nanostructured eye drug film “GlazAvir” has been synthesized for the prevention and treatment of viral eye diseases.

## 3 RESULTS

Another area of new MP research is the formation of metal nanoparticles with bactericidal and bacteriostatic properties in the structure of a polyanionic carrier polymer, Na-carboxymethylcellulose. As 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 AgCMC solutions in excess of Ag+-ions. By varying the ratio of the reactant components, their concentrations and reaction parameters, the solutions, hydrogels, films and MP powders containing spherical and rod-like silver nanoparticles with sizes of 5-25 nm were obtained. Stabilization of silver nanoparticles in the structure of the polymer matrix is explained by the enveloping of silver particles by polyanion macromolecules capable to interrelation. The obtained MP shown high biological activity against a wide range of bacteria and fungi [33-38].

## 4 CONCLUSION

Based on the above, it can be concluding that the creation of new MP relates to the developing field of chemistry, biology and pharmacology of high-molecular compounds. The basic principles for the creation of new MP, considered in this report, may be consider in the molecular design of polymer forms of biologically active compounds. Advances in MP synthesis apparently related to the experimental elucidation of MP action mechanisms and the choice of purposeful ways and approaches to their synthesis. Advances in new MP 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 MP fine molecular structure and the effect of their biological activity, the realization of targeted MP transport to target organs, and mechanisms of MP and DS penetration into the cell. It the creation of new MP, a large value is assign to the covalent bond formation between MP and carrier polymer. In contrast to DS, for MP, 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 MP with macromolecules have a cooperative nature, the polymer effect manifests itself, while the structure regularity for achieving the resulting polycomplexes stability between MP and the organism is the determining factor. Structural heterogeneity of MP can often lead to various biological effects, including the manifestation of toxicity. Stereochemistry and chain-length distribution of polymer is playing an important role in manifestation of MP biological activity. For polyanions, it has been established that biological activity and toxicity are the function 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 MP development. Thus, it can be concluding that MP and practical possibilities of their creation are unique in many cases and can be not achieve by low-molecular DS using.

## REFERENCES


[1] Shtilman M.I. Biomaterials are an important area of biomedical technologies // Herald of RSMU, 2016. No. 5.

[2] Vasiliev A.E. Medicinal polymers. The results of science and technology, 1981. volume-16. from. 3-119.

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

[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, 2011, XI, 180-184

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

[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. 3.3 (52), 2012 S.432-437 AcadSci book "Russia.

[7] Sidebotham R.L. "Adv. Carb. Chem., 1974, 30, 371-444.

[8] Rembaum A. "Applied Polymer Symp.", 1973, No. 22, 229-317.

[9] Ferutte P. "IeFarmaco, Ed. Sci. ", 1977, 32, No. 3, 220-236

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

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

[12] Butler G.B. "J. Polymer Sci., Polymer Symp. " 1975, No. 50, 160-180.

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

[14] Breslov, D. S. "Pure Applied Chem.", 1976, 46, No. 2-4, 103-113.

[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, 1978, p. 263-303.
[16] Levy H. B., Ibid, p. 305-329.
[17] Regelson W. "J. Polymer Sci., Polymer Symp.", 1979, No. 66, 483-538.
[18] Sarymsakov A.A., Yunusov Kh.E., Atakhanov A.A., Rashidova S.Sh., "Medico-biological polymers and prospects of their creation" Pharmaceutical Journal, 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: Volume 47, Issue 3 (2011), Page 415-418
[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, 2014, Vol. 83, No. 6, pp. 751-753. © Pleiades Publishing, Ltd., 2014.
[21] Regelson W., Holland J. F. "Nature", 1958, 181, No. 4601, 46-47.
[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., 6061 p.
[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.
[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., 10-11 p.
[25] Kudyshkin V.O., Futoryanskaya AM, Milusheva R.Yu., Kareva N.D., Rashidova S.Sh. Synthesized graft copolymers of chitosan Bombyxmori and N- vinylcaprolactam. // DANRU, №2, 2010 C.60-63.
[26] Rashidova S.Sh., Milusheva R.Yu., Yugay S.M. "Nanomaterials Based on Chitosan of Bombyx mori", Advances in chitin science, 2011. XI. 230-235.
[27] Milusheva R.Yu., Song W., Rashidova S.Sh. // Bionanocomposites Based on Chitosan of Bombyx Mori and Sepiolite Pangel S9, Advances in chitin science, 2011, XI, 132-133.
[28] Sarymsakov AA, Li Yu.B., Rashidova S.Sh.. Eye medicinal films for the treatment of viral diseases of the eye. Korean Newsletter "Tinbo", 2014
[29] Ershov F.I., Sarymsakov A.A., Nesterenko V.G., Rashidova S.Sh. and etc. Patent of the Russian Federation No. 2270708, 2003; No. 2002755, 1993; No. 21478, 2000.
[30] Ringsdorf H. In: "Polymeric Drug Delivery Systems". Ed by Kostelnik B. N. Y., Gordon Breach, 1978, p. 197.
[31] Trouet A. In: Polymeric Drug Delivery Systems. Ed by Kostelnik B. N. Y., Gordon Breach, pp. 157-173.
[32] Sarymsakov A.A., Rashidova S.Sh., Aripova T.U. "New in the prevention and treatment of influenza and ARVI", Tashkent 2010, pp. -110
[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, 2015. P. 270-273
[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 № 3. P.370-373.
[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, 2011. - P.128-145.
[36] Yunusov Kh.E., Atakhanov AA, Sarymsakov AA, Rashidova S.Sh., Lobanova K.V., Tashpulatov Zh.Zh. Nanoparticles of silver, formed on polymer matrices and their bactericidal properties. Pharmaceutical Journal, №1, 2010, p. 55-59.
[37] Oksengendler BL, Turaeva N., Maksimov SE, Dzhurabekova FG, Peculiarities of the radiation defect formation in nanocrystals embedded in a solid matrix, ZhETF, v.138, issue 1 (7), 1- 6 (2010).
[38] Mailoa, M. N., Mahendradatta, M., Laga, A., & Djide, N. (2013). Tannin extract of guava leaves (Psidium guajava L) variation with concentration organic solvents. International Journal of Scientific & Technology Research, 2(9), 106-110.http://www.ijstr.org/final-print/sep2013/Tannin-Extract-Of-Guava-Leaves-Psidium-Guajava-L-Variation-With-Concentration-Organic-Solvents.pdf