BIOMATERIALS ARE AN IMPORTANT AREA OF BIOMEDICAL TECHNOLOGIES

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The review describes the use of biomaterials (polymeric biomaterials in particular) in the development of medical and biological products and devices, such as implants and endoprostheses; components of bioactive and pharmaceutical agents; carriers for bioengineering applications; sorbent agents and membrane systems used for the purification and separation of biological media; artificial biocatalysts, and general purpose biodegradable products. This review is provided with a short reference list of relevant monographs and reviews predominantly by Russian authors.

Keywords: artificial materials, biomaterials, polymer, endoprosthesis, implant, biodegradation

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БИОМАТЕРИАЛЫ — ВАЖНОЕ НАПРАВЛЕНИЕ БИОМЕДИЦИНСКИХ ТЕХНОЛОГИЙ

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Обзор посвящен использованию биоматериалов, преимущественно полимерных, для создания изделий и препаратов медико-биологического назначения — имплантатов и эндопротезов; компонентов биологически активных и лекарственных препаратов; носителей, предназначенных для использования в биоинженерных методах; сорбентов и мембранных систем, применяемых для очистки и разделения биологических сред; искусственных биокатализаторов; биодеградируемых изделий общего назначения. Обзор снабжен кратким списком литературы, состоящим в основном из монографий и некоторых обзоров в данной области, изданных преимущественно на русском языке.

Ключевые слова: искусственные материалы, биоматериалы, полимер, эндопротез, имплантат, биодеградация

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In the international literature, materials that interact with living tissues, organs and organisms are commonly referred to as “biomaterials”. The methods of their production, research and application have been actively evolving in recent decades. To a large extent they determine the current level of development of such areas of knowledge as medical science, pharmaceutics, cosmetics, biotechnology, agriculture, and food industry (life sciences and technologies).

There are scientific journals on biomaterials that generally have a very high impact factor, namely *Biomaterials, International Journal of Biomaterials, International Journal of Polymeric Materials and Polymeric Biomaterials, Journal of Biomaterials, Journal of Biomaterials Science, Journal of Biomedical Materials Research, Journal of Biotechnology and Biomaterials, Journal of Controlled Release, Advances in Materials Science and Engineering, Journal of Functional Biomaterials, Journal of Materials Science: Materials in Medicine*, and others. A number of international encyclopedias and reference books have been published covering various issues related to biomaterials, such as [1, 2]. A high-quality textbook *Biomaterials Science* underwent 3 editions (in 1996, 2004, and 2013) and is recommended for the US universities [3]. The following international and national societies work actively to develop this area of science, conduct international conferences and congresses, and publish their own journals: International Society for Biomedical Polymers and Polymeric Biomaterials, International Union of Societies for Biomaterials Science and Engineering, International Society of Controlled Release, Society for Biomaterials (US), European Society for Biomaterials, Canadian Biomaterials Society, UK Society for Biomaterials, and others. The size of the global biomaterials market has become quite noticeable (see the table below).

The development, research and manufacturing of medical and biological supplies and products are regulated by GMP (Good Manufacture Practice) standards. Despite the fact that metals, carbons, inorganics and composites are important members of the biomaterials family, polymers are particularly special as it is possible to obtain polymer-based articles and agents that not only have the required physical and technical characteristics, but also can swell and dissolve in water, which is unnatural for other groups of biomaterials. As a rule, polymeric biomaterials are produced in relatively small quantities, but they are significantly superior to other groups of the polymeric materials in terms of range and diversity of properties [4].

The field of biomaterials is a prominent interdisciplinary field where the achievements of chemistry, physics, medicine, biotechnology, metallurgy, and electronics are applied. This

The size of the global market of biomaterials and biomaterial-based products

Object	Market size. $ bln	Annual growth. %	Source
Biomaterials	62.1 (2015) 115.2 (2020)	+10.3	[ResearchMarket. 2016] [MarketInteligence. 2016]
Implants	70.8 (2015) 115.8 (2020)	+10.3	[Allied Market Research. 2016]
Materials for treatment of wounds and burns	11.9 (2015) 20.5 (2020)	+ 8.0	[Allied Market Research. 2016]
Medical adhesives and cements	6.9 (2015) 14.2 (2022)	+10.7	[Medcajet.2016]
Catheters	70.8 (2015)	+10.6	[Allied Market Research. 2016]
Materials for cell and tissue engineering	11.9 (2015) 45.5 (2022)	+21.0	[SmitheryApex. 2016]

determines the aspects of training of specialists who plan to work in this field. Currently, specific undergraduate and master degree programs are available in more than 250 universities around the world (mostly in the US). In Russia the master degree programs are available in D.Mendeleev University of Chemical Technology, St. Petersburg Polytechnic University, Siberian Federal University (Krasnoyarsk), Moscow State University of Design and Technology.

Several most important applications of biomaterials can be distinguished [5]:

– materials for implants and endoprostheses, including biodegradable endoprostheses used in cardiovascular surgery, bone surgery, ophthalmology, and dentistry, in soft tissue replacement and wound and burn treatment, in the production of resorbable suture material, etc;

– materials for systems with biological, especially medicinal, activity;

– materials for bioengineering (cell, tissue and genetic) technologies used as carriers and scaffolds for living tissue growth and delivery of genetic material into the cell;

– materials for the separation (usually sorption and membrane) systems that find their application in medicine and biology and used in hemodialysis and hemosorption devices, including those with electrosensitive coating;

– materials for biochemical analysis and synthesis used in microarrays and carriers for polypeptide and polynucleotide synthesis;

– materials for systems with enzymatic activity that contain immobilized enzymes, organelles and cells;

– materials for products that do not come into direct contact with blood and lymph, for example contact lenses and devices for external osteosynthesis;

– general purpose biodegradable materials, including those that can be degraded by microorganisms after use.

Polymeric implants [4–9]

Polymeric materials are a base for many groups of implants — objects implanted into the body by surgical methods where they "work" fully or partially surrounded by living tissues. The implants that replace removed internal organs or their fragments are commonly referred to as endoprostheses.

Depending on how well the implant material can decompose exposed to the surrounding environment, either a gradual decrease in the weight and volume of the objects implanted into body (biodegradation) is observed or, in case of indecomposable or slowly decomposable material, the thin tissue membrane (capsule) is formed around the implant, which is a protective reaction of the organism to a foreign object [10–17].

Currently, implants are widely used in surgery. The largest group of implants is the implants used in cardiovascular surgery, bone and soft tissues surgery, ophthalmology, and dentistry. Some implant groups comprise various products used in patients with skin defects, including wounds and burns, and those used as suture materials, etc.

Implants for the cardiovascular system [18–27]

For the manufacturing of cardiovascular implants that contact with blood (endoprostheses of vessels, cardiac valves, or the whole heart, circulatory support systems, such as endoprostheses of the left ventricle, pulsating balloons implanted into the aorta, coating of electric cardiac pacemaker leads), high hemocompatibility materials are used. These materials must not induce destruction and denaturation of the molecular and cellular components of blood, affect the salt and water balance and blood pH, or trigger formation of blood clots (thromboresistance).

Among the polymers with improved hemocompatibility, the "segmented" polyurethanes have found their practical application (such as block copolyurethanes with flexible blocks, e.g. polyether or polyester resins, polycarbonates, polysiloxanes, and blocks that ensure good intermolecular interaction), as well as polyethylene terephthalate, fluorine-containing carbon-chain polymers (expanded polytetrafluoroethylene, fluoron), polysiloxanes, and carbon-bearing composites.

But the search for materials with even better hemocompatibility is going on. The most promising here are hydrogel-coated surfaces, surfaces with immobilized thrombolytics and anticoagulants, and endoprosthesis surfaces with immobilized endothelial cells.

Examples of the prostheses used in cardiovascular surgery are shown in Fig. 1–3.

Implants for the skeletal system [1, 3, 6, 9, 28, 29]

Implants are also widely used in bone surgery for the replacement of damaged or removed parts of bones, elements of structures of artificial joints, fixators for fracture repair in osteosynthesis. For their manufacturing, polymers and composites with carbon and inorganic fillers, such as hydroxyapatite, are used.

Polymers used in bone implants must either possess high resistance to biodegradation (e. g., polymers used for joints endoprostheses), or decompose if the goal is to gradually replace the implant with living tissue (e. g., fixators for internal osteosynthesis, sealing compounds).

Among non-biodegradable polymers used to create bone implants, ultrahigh-molecular-weight polyethylene, polysulfones and polyformaldehyde are worth mentioning. Polyesters of hydroxycarboxylic acids, especially glycolic, lactic and hydroxybutyric, and their copolymers, are becoming increasingly important in the manufacturing of biodegradable implants that form non-hazardous metabolizable fragments when decomposing inside the body.

Polyacrylates (the so-called acrylic cement), poly-α-cyanoacrylates, and copolyurethanes serve as a polymeric base for adhesives and cements used for the attachment of endoprostheses of joints and bone fragments.

Fig. 4 and 5 show the examples of prostheses of hip and knee joints

Soft tissue implants [5, 7]

The best-studied implants for soft tissue replacement are breast endoprostheses - polysiloxane rubber bags with soft filler injected through the catheter before or after implantation. Despite the mass use of such implants, the filler issue has not been completely solved, as polysiloxane gels, oil emulsions and saline solutions used in some implants have certain drawbacks in terms of safety and mechanical characteristics.

For the filling of postoperative cavities in soft tissues, elastic materials, including expandable and hydrogel materials (polysiloxanes, polyurethane foams), are used. For the replacement of some internal membrane elements, for example, during the repair of the abdominal and thoracic walls, the use of polymeric mesh was suggested; once the mesh (polyolefin or expanded polytetrafluoroethylene) is placed inside the body, connective tissue starts to gradually grow through and around it.

The adhesives for soft tissue bonding during or after surgery are not widely used yet, although PEUR-, cyanoacrylate-, and protein-based adhesives developed for this purpose show good results in some cases. Among the known disadvantages of such systems are difficulty to provide a sufficient level of adhesion and hardening impeded by intense water supply to the bonded tissue, and low bonding strength.

Certain groups of biomaterials implanted into the soft tissues comprise soft polymeric implants, injectable polymeric systems for cosmetic purposes, and polymeric mesh.

Endoprostheses of ligaments and tendons [5, 7]

Endoprostheses of ligaments and tendons are of great importance in orthopedic surgery. Here, porous tapes of

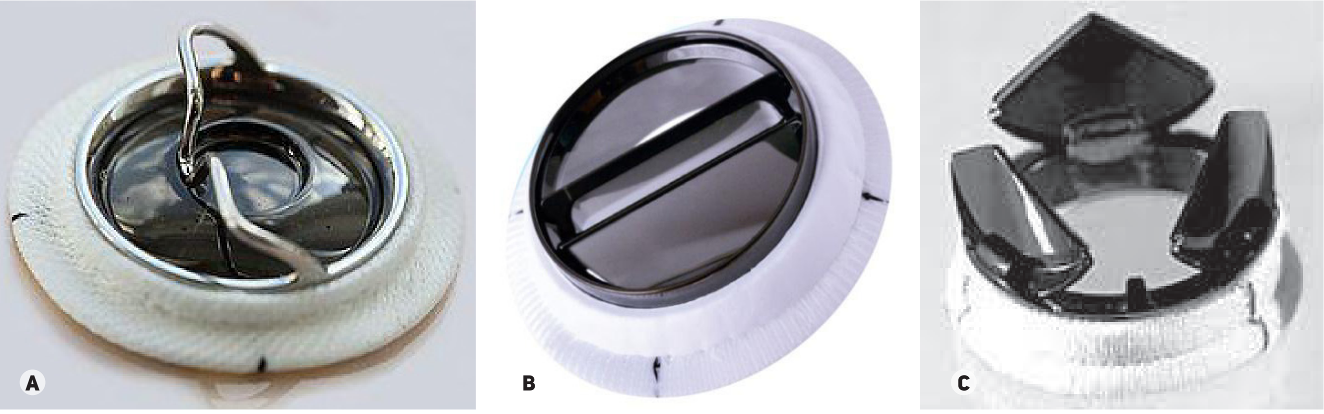

Fig. 1. Examples of structural heart valve endoprostheses: **(A)** disc endoprosthesis (Specialnoye konstruktorskoe buro medicinskoy tematiki, Russia); **(B)** bi-valved endoprosthesis (MedInzh, Russia); **(C)** three-valved endoprosthesis CorBit (Bakulev Scientific Center of Cardiovascular Surgery, Russia)

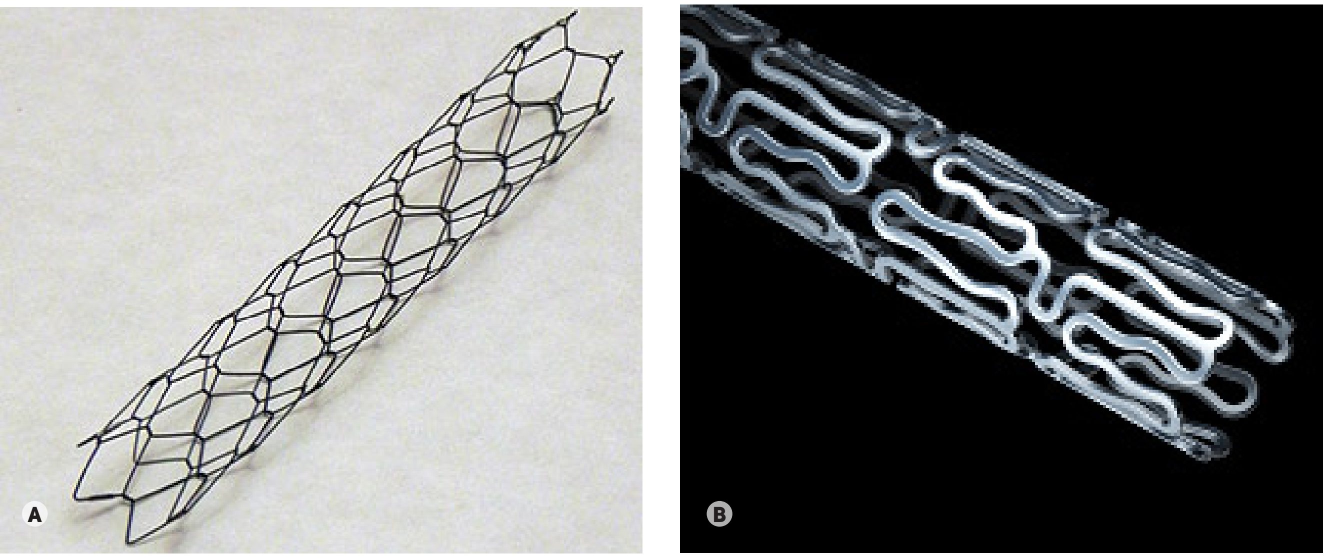

Fig. 2. Examples of vascular stents: **(A)** self-expanding wire stent Alex (Komed, Russia); **(B)** MULTI-LINK VISION Coronary Stent made with laser processing of a tube of an alloy of cobalt and chromium (Abbott Vascular, USA)

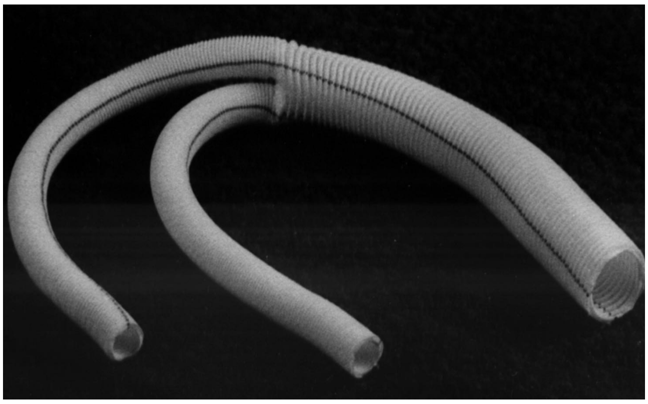

Fig. 3. Woven crimped bifurcation vessel endoprosthesis made of PET - fluorlone (PGTO Sever, Russia)

Fig. 4. Parts of the hip endoprosthesis by Endo Plus (UK)

Fig. 5. Parts of the Consensus knee prosthesis by Hayes Medical (USA)

polyethylene terephthalate and foamed polytetrafluoroethylene have found their application. The use of biodegradable polyesters of hydroxycarboxylic acids for the replacement of ligaments and tendons is actively studied. Such endoprostheses are designed to be replaced by living tissue.

It should be noted that muscle tissue endoprostheses have not been developed yet, although there are a number of studies on polymers that change their size depending on the electrical and physical characteristics of the environment.

Coatings for wounds and burns [5, 7]

Much effort has been made to create effective coatings for wounds and burns. The complexity of the problem is mainly determined by the fact that different stages of the healing process require materials with different combinations of characteristics (gas-permeable film and disperse sorbent, isolating and biologically active materials). However, the industry produces a significant range of such materials, including those containing several polymeric layers with different functions, in which various combinations of polymers, such as silicone block copolymers, polyesters of hydroxycarboxylic acids, PEUR, polyvinyl alcohol, alginates, collagen, chitosan, chondroitin sulfates, and some of others are used.

Polymeric implants in dentistry [5, 7]

Polymeric filling materials are a good example of how polymeric implants can be used in dentistry. Of particular interest are various hardening low molecular weight or oligomeric systems that contain unsaturated (meth)acrylate groups, epoxy compounds, and transition metal polycarboxylate complexes. At the same time, it should be noted that currently existing dental endoprostheses are made from metals and inorganic biomaterials.

Implants in ophthalmology [5, 7]

Polymeric implants have important role in ophthalmology. Thus, eye lens implants have found their application here, namely: monofocal and multifocal intraocular lenses made from polymethylmethacrylate and acrylate copolymers, and silicone materials; implantable contact lenses and intracorneal segments from polymethylmethacrylate, copolymers of collagen and acrylates; devices that reduce the intraocular pressure — shunts (silicone tubes) and valves manufactured from polyolefins, polymethylmethacrylate, and cross-linked silicones.

Suture materials [5, 7]

A separate group of widely used implants is comprised of suture materials, or rather, their filar component. The kits of suture filaments that usually contain functional polymeric coating in addition to the multifilament part are produced by many firms. Currently, sutures from both non-biodegradable polymers (polypropylene, polyamides, expanded polytetrafluoroethylene, polyethylene terephthalate, silk, cotton, flax) and biodegradable materials (catgut, polyesters of hydroxycarboxylic acids) are widely used. The polymeric coatings of suture filaments (polysiloxanes, copolymers of ethylene oxide and propylene oxide, copolymers of N-vinylpyrrolidone and acrylates) contain dyes, haemostatics and antimicrobial agents.

Polymers in the bioactive systems [30–40]

Polymeric biomaterials are used to create systems with different biological activity, i. e. the ability to affect biological objects, including the human body, by regulating their vital functions through stimulation, inhibition or development of certain features. The extreme manifestation of the biological activity is the biocidal action, when exposure to a substance (biocide) leads to the object's death.

Bioactive systems with polymeric components or fragments are designed for implementing various types of activity: they can stimulate biological processes or inhibit them and have biocidal properties. Such systems can be divided into two groups; the first comprises forms with non-chemically incorporated bioactive substances (BAS), the second comprises polymeric bioactive substances.

Forms containing BAS that have no chemical bonds with polymers

Systems containing polymers in which bioactive substances have no chemical bonding with polymeric components are widely used in medicine. Such systems are insoluble in water, and the incorporated active substance enters body tissues owing to diffusion or system decomposition, including erosion. We can divide such products into two groups: those in which polymeric components do not affect the rate of BAS release and those in which polymeric components determine the rate of BAS release.

The examples of polymeric components that do not affect the rate of BAS release are powdered polymeric fillers of tablets, components facilitating their molding and ensuring they do not stick to molds. Here, starch, polyvinyl alcohol and other biologically neutral polymers are commonly used

The forms with non-chemically added BAS become increasingly important; here, the polymeric component determines the rate of BAS release to living tissues. Such insoluble systems, as well as polymers from which BAS is released due to the gradual degradation of its chemical bonding with a polymeric carrier (to be described later), are commonly referred to as systems with controlled release of the active substance. These systems can eliminate or reduce the impact of a narrow range of doses and concentrations required for producing a desired effect, which is beneficial for the patient, because excesses can lead to adverse reactions as the medication is not only delivered to the target organ, but also distributed throughout the body providing acute toxic, allergenic and carcinogenic effects. This complicates accurate dosing of the BAS. In addition, adverse reactions do not allow administering such amounts of BAS that can provide a long-term effect. With BAS susceptible to leaching, volatilization or biodegradation (which is often observed when using pesticides) and structural changes (typical for protein drug compounds), a positive effect is achieved through the use of excessive doses of the medication or its multiple administration, which considerably increases the costs.

The principle of controlled release is used in many forms of BAS. Thus, tableted forms of medications are widespread and well-known. They are most often used as preparations for enteral administration, but tableted forms for subcutaneous implantation are also known.

Polymeric tablet coatings delivering the drug to the desired area of the gastrointestinal tract have become widespread. For example, polymers used to create such coatings, marketed as Eudragit (Germany), contain ionogenic groups that determine the solubility of polymers in the environments with different pH. Thus, tablets coated with a polymer containing basic groups, for example copolymers of dimethylaminoethyl methacrylate with methyl or butyl methacrylates decompose in the acidic environment of the stomach. At the same time, tablets coated with polymers that contain acidic groups, for example copolymers of acrylic acid and ethyl methacrylate or metacrylic acid and methyl methacrylate, are stable in the stomach and decompose in the intestinal tract where pH ranges from 7.2 to 9.0.

Prolonged effect of the medication and reduced adverse reactions (unpleasant smell or bitter taste) make it possible to manufacture it as micro- and macrocapsules.

Widespread are various macromolecular systems in which the BAS is incorporated in the polymeric mass, from where it enters the body due to diffusion or after the gradual dissolution of the carrier. BAS-containing polymeric medicated films are used in ophthalmology for the prevention of coronary disease. They are storable and easily attach to the mucosal surface of the eye and gum (transmucosal preparations). For drug delivery, other polymeric systems are used, which work in a similar manner, for example coatings of suture materials or BAS-containing fibers themselves, catheters with antiseptics introduced into the polymeric mass, and others.

Transdermal systems (multilayer therapeutic systems glued to the skin) are one of the most promising forms of polymer-based drug substances used in adhesive patches and special devices. In general, the transdermal systems consist of an upper coating layer; a diffusion layer or a BAS- containing reservoir; a polymeric film that controls delivery of the active substance by diffusion; an adhesive layer that retains the system on the skin and ensures a direct contact with it; and a protective film of the adhesive layer removed before the system is glued to the skin. The diffusant is released from the BAS system, penetrates through the skin, reaches the subcutaneous blood vessels and spreads throughout the body.

Recently, a great deal of attention has been paid to nanosized carriers of medications, especially, liposomes, including modified amphiphilic polymers, nanospheres, dendrimers, and nanoaggregates. The optimal administration routes of colloidal systems that contain nanoparticles are injections (e.g., intravenous), inhalation, and oral administration. Nanoparticles are also used in eye drops.

Under development are BAS delivery systems that can function under specified conditions or in response to environmental conditions. Such systems are referred to "smart" or "intelligent" systems, or feedback-based systems. To some extent, they simulate the processes occurring in the body and can be physiologically optimal therapeutic systems if adjusted properly.

Another approach ensuring the delivery of a drug to the affected organ is based on introducing ferromagnetic substances to the drug followed by the exposure of the organ to the magnetic field.

It should be noted that the polymers with controlled release of BAS are used not only in medicine. Examples of such polymers are fertilizers encapsulated in a polymer shell that considerably reduces their consumption, fumigation devices and prolonged release forms of pheromones used in insect traps, and polymeric antifouling paints used to coat bottoms of ships.

Bioactive polymers

Of great importance are polymers whose bioactivity is determined by their macromolecular nature. In some cases they mimic natural polymers and can be used to replace natural components of blood. A good example here is macromolecular components of blood substitutes. Such polymers mimic two important functions of blood proteins: they maintain blood osmotic properties (components of antishock substitutes or blood substitutes with a hemodynamic effect) and ensure formation of complexes with toxic substances that enter the bloodstream (components of blood substitutes with a detoxifying effect). Oxygen carriers and their polymeric forms (modified hemoglobin) are also used as blood substitutes.

Blood substitute components are used as water-soluble non-ionogenic polymers. Polymers used to obtain components of blood substitutes with a hemodynamic effect must have a sufficiently high molecular weight (at least 50-60 kDa). Here, polymers of natural origin can be used as a base after certain chemical modification that can decompose inside the body and then be excreted from it. They include dextran, partially hydroxyethylized starch and denatured protein gelatin derived from collagen.

The polymeric components of blood substitutes with detoxifying properties are polymers with a molecular weight of about 10 kDa. They are easily excreted in the urine, so in these products the carbon-chain polymers are used, such as poly-N-vinylpyrrolidone (Hemodez and Neohemodez by Biohimik, Russia), poly-N-(2-hydroxypropyl)methacrylamide (Duxon, Czech Republic), and polyvinyl alcohol (Polidez by Himitek, Russia). These polymers exhibit strong toxicant-complexing properties.

It should be noted that the production volume of the polymeric components of blood substitutes with hemodynamic and detoxifying effects exceeds the production volume of other medical polymers.

Water soluble polyelectrolytes, polymers with cationic, anionic, and N-oxide groups also exhibit biological activity, such as microbicidal, adjuvant, coagulant, or anticoagulant; among them is polyoxidonium (copolymer of N-oxide 1,4-ethylene piperazine and (N-carboxyethyl)-1,4-ethylene piperazine bromide) that has immunomodulating properties and can be used as an adjuvant for synthetic vaccines.

We should also mention a few high-molecular compounds in which BAS or a group determining the activity of the substance are linked with the polymer by a chemical bond that does not break as the system is being used. Among such compounds are stabilized (immobilized) enzymes, including those used for the formulation of water-soluble drugs. Bound to a polymeric carrier or a modifier, the enzyme becomes more resistant to denaturation; for insoluble forms, such binding allows the enzyme to participate in the enzymatic process multiple times. The best studied are products based on dextran-modified enzyme streptokinase (Omela, Russia) used as an effective fibrinolytic agent.

Another example of systems with permanent bonding (immobilization) is a group of immunoactive polymers that are conjugates of a polymeric carrier and active, usually low molecular weight group (hapten) that stimulates receptors of immune cells. The research in this area led to the development of a series of vaccines - conjugates of polyoxidonium with a number of antigens, such as hemagglutinin and neuraminidase of three influenza viruses: A (H1N1 and H3N2) and B (Grippol by NPO Petrovax Farm, Russia), timothy grass pollen allergoid (Timpol), birch pollen allergoid (Berpol), and wormseed pollen allergoid (Polpol).

Bioactive polymers

Significant disadvantages of low molecular weight drugs, bio-regulators and biocides are their nonoptimal doses and concentrations, limited action period, rapid incidental consumption, and insufficient solubility, all of which can be eliminated or considerably reduced by using BAS in the form of a chemical compound hydrolysable over time, with polymer-based carriers or modifiers. Such chemical compound is actually a new bioactive polymer whose chemical structure differs from that of the original polymeric carrier. The chemical bond between the BAS and the polymeric carrier may degrade at a certain rate, usually by hydrolysis, sometimes involving enzyme systems. The rate of this gradual (prolonged) release can be controlled by the polymeric structure or the structure of a biologically active system. Therefore, such systems, as well as previously discussed forms with regulated BAS release, can be called systems with controlled BAS release (controlled release systems).

In contrast to insoluble drug formulations, polymeric BAS derivatives can be produced in the water-soluble form, which determines broad possibilities for their use. In these systems, controlled release of an active substance provides for the long action of the medication without overdosing and therefore side effects. Production of polymers that ensure target delivery of the medication to the affected organ is a major area of development of new systems with controlled release of an active substance.

Derivatives of poly-N-vinylpyrrolidone, poly(N-2-hydroxypropyl) methacrylamide, polyvinyl alcohol and dextran are often used as polymeric carriers for the described group of systems.

It should be noted that in addition to polymers with therapeutic properties, there are systems that exhibit bioregulatory or biocidal activity against other groups of organisms; for example, they regulate plant growth or have fungicidal properties [41-43].

Polymers in bioengineering [44, 45]

The processes and methods falling within the concept of “bioengineering” are principally aimed at optimizing the vital function of cellular systems in order to obtain practically valuable producers and tissues that can be used for the replacement of tissues and organs. Practical implementation of bioengineering methods relies to a large extent on the use of various polymeric carriers and substrates. Although the methods related to bioengineering are subdivided into cell, genetic and tissue engineering, in actual practice they often complement each other.

Cell engineering represents a field of biotechnology and is based on the cultivation of cells and tissues capable of producing the required substances in vitro (outside the body). Cell culture is often performed using porous microcarriers, such as derivatives of DEAE-dextran or sephadex (cross-linked dextran). Interior cultivation of cells can be implemented if cells are encapsulated in semipermeable polymeric microcapsules whose shell (cross-linked polylysine, agarose) allows nutrients to get through.

Tissue engineering aimed at cell culture for the regeneraion of damaged or lost tissues is one of the most promising areas of medicine and is based on the formation of the desired tissue structure from the cells seeded on a specific substrate (stem cells in particular).

As a discipline, tissue engineering was based on projects aimed at creating “artificial” tissues and organs and research on transplanting cells and biologically active components to the carriers to repair lesions in various tissues of the body. The basic principle of this approach is the development of biodegradable carriers combined with donor cells and/or bioactive substances and their implantation into the damaged organ or tissue. To grow the tissue in the body, the cultured cells must stay on the carrier for some time: when its biodegradation is too rapid, the cells can be washed from it with the body fluids. On the other hand, if the substrate “lives” for too long, it interferes with the normal process of tissue or organ regeneration. Among the polymers satisfying the described requirement are polyglycolide, polylactide, copolymers of glycolic and lactic acids, polycaprolactone, polypropylene fumarate, polyanhydrides, and polyorthoesters.

Genetic engineering makes use of the achievements of such sciences as molecular biology, cytology and genetics and is similar to targeted drug delivery in terms of nature of scientific approaches and techniques, since its ultimate goal is the delivery of nucleic acids or their fragments into the cell. The most appropriate technique for delivering the genetic material into the cell is endocytosis of its complexes with polymeric carriers, usually polycations (polyethyleneimine, polylysine and others). This method (transfection) has significant advantages over other methods of genetic material delivery, such as sonoporation, electroporation, microinjection, or the use of viral carriers. The most advanced biological objects in which genetic engineering techniques can be applied are microorganisms and plant cells, although there have been a number of works recently in which genetically engineered animals were used. For humans, genetic engineering can be an effective remedy for genetic disorders and predisposition to certain diseases.

Polymers in biocatalytic processes [46–49]

Development of artificial biocatalysts based on modified enzymes is of great importance for medical bioengineering or systems for bioanalysis, as noted in this review in the relevant sections. Besides, these biocatalysts play a very important role in industrial biotechnology. This is due to the significant disadvantages of enzymes extracted from living tissues, in particular the instability of their globular structure in response to various influences (susceptibility to denaturation). This applies to both simple and complex enzymes that have a non-protein component (coenzyme) in their structure, in addition to protein components. Another significant technological disadvantage of enzymes is their solubility in water, which participates in most enzymatic industrial cycles and hinders enzyme separation after the process is completed and its further re-use.

Those disadvantages were to a large extent neutralized by binding the protein macromolecule of the enzyme to the insoluble carrier that can be quite easily separated from the reaction mixture and re-used in stirred-tank reactors or column reactors in continuous processes. Furthermore, the binding of the enzyme macromolecule to the carrier increases its conformational stability and stabilizes it in the presence of denaturing factors.

The carriers used to obtain immobilized enzymes come in various forms, such as granules, fibers, membranes intended for filling columns, helices, rings, tissues, etc. Although for the manufacturing of such carriers, especially granular, inorganic materials are also used, most of the industrial carriers for immobilized enzymes are made from polymers or their composites with inorganic materials.

To date, a significant number of methods of binding of enzyme macromolecules to a carrier have been developed. They are based either on enzyme adsorption on the carrier surface, chemical binding of a protein globule to the functional groups of the carrier, or its inclusion into the polymeric mass of the carrier. Protein inclusion in polymeric mass is used for the formation of fibers and films (membranes) that must exhibit enzymatic activity.

The cells themselves can be used as biocatalytic systems if they are immobilized, primarily by microencapsulation or inclusion into hydrogel granules (derived from agarose or polyvinyl alcohol, etc).

Polymers in the separation processes [5]

The processes of sorption and membrane separation, used in a variety of technologies, have found wide application in medicine and biology. In addition to the isolation and purification of products of various biotechnological reactions, they are used for the purification and detoxification of biological fluids, such as blood and lymph.

Polymeric biomaterials used in these processes come in direct contact with blood or lymph and must be highly hemocompatible Just as polymeric implants that “work” in the blood stream, they must not cause blood clots, injure formed elements, cause denaturation of the protein components and release toxic compounds.

The membrane method of blood purification (hemodialysis and hemofiltration) performed in hemodialyzers consists in removing harmful substances and toxins from the blood, when the dialyzable liquid (blood) flows by one side of the polymeric membrane and the dialysis fluid flows by the other side. When using ultrafiltration membranes, low- and medium molecular weight substances pass through them under the influence of a concentration gradient, but high-molecular weight components of blood do not pass through. If the dialysis fluid pumped in counterflow to the dialyzable liquid is replaced with fresh fluid quite frequently, harmful substances can be removed from the dialyzable liquid.

Polymeric ultrafiltration membranes are also used for blood oxygenation carried out in the oxygenation unit cells of the “artificial heart-lung” machine. Here, blood flows by one side of the membrane, and a gaseous medium enriched with oxygen flows by the other side. Thus, due to the difference in the partial pressure, oxygen enters the blood stream. Carbon dioxide passes through the membrane in the reverse direction. This device is indispensable in surgeries performed on the cardiovascular system.

Membrane separation is also used for the decontamination of drug solutions, when methods of stronger impact on the disinfectant, such as heat or radiation sterilization, are not applicable.

Sorption is used to purify various biological fluids: blood (hemosorption), blood plasma (plasmasorption), lymph (lymphosorption), lymph plasma (plasma-lymphosorption). The sorbents used in such processes are granular or powdered systems that are usually subdivided into nonselective, capable of absorbing several substances, and selective used for extracting specific sorbates.

Selective sorbents are polymeric systems containing functional groups that ensure ion exchange or biospecific binding to the extractable substance, including immune sorption.

A separate type of sorption decontamination processes is enterosorption related to the use of sorbents that extract toxins from the gastrointestinal tract. For this purpose, the sorbents based on activated carbons are used, as well as polymeric sorbents based on lignin, cellulos and crosslinked polyvinylpyrrolidone.

Polymers in bioanalytical systems and synthesis of biopolymeric analogues [5]

The use of polymers in various bioanalytical devices and medications is extremely important for the development of medical and biological sciences and technologies. It should be noted that application of polymers in biomedicine is determined not only by the specific branch of this science, but also by the fact that polymer-based devices for bioanalysis come in direct contact with living tissues, such as biological fluids and cell suspensions.

Among the research methods used in biochemistry, biology and medicine are bioanalytical methods, such as electrophoresis and immunoelectrophoresis (on plates, discs, in columns and capillaries), that make use of polymeric carriers, such as agarose and polyacrylamide gels and their modifications; various chromatographic methods based on the use of polymeric sorbents, including affinity- and immunosorbents; enzyme immunoassay that makes use of polymeric substrates; latex agglutination test systems based on the "curdling" of polymer latexes derived from polymeric microspheres whose surface is modified by a component of the antigen-antibody pair.

Polymers are an important component of various biosensors, such as membrane-electrode devices containing immobilized enzymes. Moreover, special attention has been paid recently to the fast bioassay methods based on the use of biosensors.

Polymeric carriers are a crucial component of polypeptide and polynucleotide synthesis. Only after the discovery of solid-phase methods for their preparation, it became possible to solve extremely difficult or impossible tasks, such as separation of the products of the addition reaction from the initial products and reagents given their solubility in water, and preservation of macromolecular chains in the course of optical isomer synthesis. Also, solid-phase synthesis techniques for the preparation of polysaccharides have been developed. The evolution of this approach described in many publications enabled to obtain a large number of synthetic polypeptides and polynucleotides, and in many cases their synthesis was automated.

Solid-phase amino acid sequencing of natural macromolecules based on the use of polymeric carriers is no less important; here, the stepwise cleavage of the terminal fragments, combined with the amino acid analysis of the biopolymer, reveals the sequence of the respective links in the macromolecule.

Biodegradable polymers of general purpose [5, 11]

In recent years, much attention has been paid to the development of biodegradable materials of general purpose. It is predicted that such environment-friendly materials will be widely used not only in medicine, but in the manufacturing of degradable packaging, disposable items, special types of clothing, etc. Several groups of such materials are worth mentioning.

Natural polymers, especially polysaccharides and proteins, and their modifications are still used as before. Cellophane remains a very popular packaging material. Composites based on acetate cellulose and starch hold some promise too.

Composites based on polyolefins and starch are promising film materials with a large tonnage capacity and a high biodegradation rate. Products based on these composites can be quickly fragmented and absorbed by soil microorganisms.

An important group of biodegradable polymers comprises polymers of hydroxycarboxylic acids, primarily polylactic acid (polylactide), large-tonnage production of which has been launched in some countries in recent years.

Non-implantable medical polymeric devices and products [5]

Among these products, contact lenses should be noted in the first place; they are manufactured in large quantities in the developed countries. Despite the fact that they are placed on the cornea, they are washed with the tear fluid and therefore must have high biocompatibility. Strictly speaking, contact lenses are not implants because they do not come in direct contact with the body liquids, such as blood and lymph. The most common materials for contact lenses are cross-linked silicone systems with good optical characteristics and high gas and vapor permeability, copolymers of 2-hydroxymethylmethacrylate and ethylenebismethacrylate, and in some cases crosslinked copolymers of acrylamide.

Polymers play an important role in the medical industry as raw materials for the manufacturing of orthopedic and dental equipment. This area of polymer application is of special interest and is not the subject of this review

CONCLUSION

As seen from this brief review, the materials and products based on the different types of high-molecular compounds are very widely used in medicine and biology. There are some specific aspects of their application that distinguish this field from other areas of chemistry and technology of high-molecular compounds. Firstly, most polymers for biomedical application are produced in small quantities or come as specially prepared and carefully purified batches of conventional polymers. In some cases, the annual demand for these polymers does not exceed a few kilograms or tens of kilograms. Secondly, many of these polymers are manufactured using small-size equipment, often made of glass, according to the principle of flexible manufacturing systems. Thirdly, since many of these products come in direct contact with a living organism, their manufacturing must meet GMP requirements. Finally, during the development of such products one should consider that they must be approved by the government agencies. These factors have a strong impact on training programs for researchers and technicians who plan to work with polymers employed in medicine and biology.

Another important aspect of this area of knowledge is related to the constant updating and improvement of the methods of application of polymeric materials and products, which necessitates a serious effort aimed to improve the structures and properties of the polymers and to develop new high-molecular compounds that meet the specified requirements.

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