SYNTHESIS AND PROCESSING OF POLYMERS AND POLYMERIC COMPOSITES

СИНТЕЗ И ПЕРЕРАБОТКА ПОЛИМЕРОВ И КОМПОЗИТОВ НА ИХ ОСНОВЕ

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REVIEW ARTICLE

Modern polymer composite materials for bone surgery: Problems and prospects

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Abstract

Objectives. *To discuss the main problems and prospects of creating modern osteoplastic materials based on polymer compositions used for bone surgery.*
Methods. *This review summarizes the research works devoted to the creation of materials used for bone implants and issues involved in their practical testing, as well as analyzes and synthesizes data of scientific articles on the following topics: rationale for the use of biodegradable materials in bone surgery; biodegradation and bioreparation bone graft processes; requirements for degradable polymer composite materials (PCMs) for biomedical applications; overview of polymeric materials suitable for use in implant practice; impact of modifications of the PCM on the structure and biological activity of the material in biological media; effect of exhaust and heat treatment on the molecular structure of polyalkanoates.*
Results. *The most promising biodegradable resorbable materials for reparative bone surgery to date are compared. The requirements for these types of materials are formulated and a rationale for their use is provided that takes into account the advantages over traditional metal and ceramic implants. The features of the kinetics and mechanism of biodegradation of implants in their interaction with the bone biological environment of the body from the moment of implant insertion to complete wound healing are considered. As a result of the analysis, factors that may affect the activity of implant decomposition and methods of adjusting the decomposition rate and mechanical characteristics of the material, such as chemical functionalization, the creation of block copolymers, the inclusion of fibers and mineral fillers in the composite, as well as heat treatment and extraction of the*

composite at the manufacturing stage, were identified. Among the main factors, the influence of the structure of the composite material on its biological activity during interaction with biological media was evaluated. Of polymer materials, the main attention is paid to the most common biodegradable polymers widely used in medicine: polyhydroxybutyrate (PHB) of microbiological origin, polylactide (PLA) and other polymers based on polylactic acid, polycaprolactone (PCL). The effect of their modification by such additives as hydroxyapatite (HAP), chitin and chitosan, and beta-tricalcium phosphate (β-TCF) is considered. Materials based on PHB are concluded as the most promising due to their complete biodegradability to non-toxic products (carbon dioxide and water) and good biocompatibility. Nevertheless, existing compositions based on PHB are not without disadvantages, which include fragility, low elasticity, unstable behavior under high-temperature exposure during processing, implant molding, sterilization, etc., which requires improvement both in terms of polymer modification and in terms of composition of compositions.

Conclusions. *The review considers approaches to achieving the properties of materials required for perfect implants. The main requirements for implants are optimization of the time of resorption of the osteoplastic matrix, facilitating the resorption of the osteoplastic matrix synchronized in time with the process of bone regeneration. To achieve these requirements, it is necessary to apply technologies that include modification of polymer composite materials by affecting the chemical composition and structure; introduction of fillers; use of chemical functionalization, orientation extraction, heat treatment. The success of using bone materials based on biodegradable polymers is based on an accurate understanding of the mechanism of action of various components of the implant composition and strict compliance with the tightening regulatory requirements of implantation technology.*

Keywords: *osteoplastic materials, regenerative medicine, tissue engineering, osteogenesis, bone implant material, biodegradable matrices, polyalkanoates, hydroxyapatite, bioactivity of bone implants, molecular structure of implant material*

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ОБЗОРНАЯ СТАТЬЯ

Современные полимерные композиционные материалы для костной хирургии: проблемы и перспективы

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Аннотация

Цели. *Обсуждение основных проблем и перспектив создания современных остеопластических материалов на основе полимерных композиций, используемых для костной хирургии.*

Методы. *Обзор суммирует научно-исследовательские работы, посвященные созданию материалов, применяемых для костных имплантатов, и их испытанию на практике, анализирует и обобщает данные научных статей по следующим разделам: обоснование использования биоразлагаемых материалов в костной хирургии; закономерности биодеградации и биорепарации костного имплантата; требования, предъявляемые к разлагаемым полимерным композиционным материалам (ПКМ) для биомедицинских применений; обзор полимерных материалов, пригодных для использования в имплантационной практике; влияние модификации ПКМ на структуру и биологическую активность материала в биосредах; влияние вытяжки и термической обработки на молекулярную структуру полиалканоатов.*

Результаты. *Рассмотрены наиболее перспективные на сегодняшний день биоразлагаемые резорбируемые материалы для репаративной костной хирургии. Сформулированы требования, предъявляемые к данным типам материалов, и дано обоснование их использования с учетом преимуществ по сравнению с традиционными металлическими и керамическими имплантатами. Рассмотрены особенности кинетики и механизма биодеградации имплантатов при их взаимодействии с костными биосредами организма от момента введения имплантата до полного заживления раны. В результате проведенного анализа были установлены факторы, которые могут повлиять на активность разложения имплантата и методы корректировки скорости разложения и механических характеристик материала, такие как химическая функционализация, создание блок-сополимеров, включение в состав композита волокон и минеральных наполнителей, а также термообработка и вытяжка композита на стадии изготовления. Среди основных факторов было оценено влияние структуры композиционного материала на его биологическую активность при взаимодействии с биосредами. Из полимерных материалов основное внимание уделено наиболее распространенным биодеградируемым, широко используемым в медицине полимерам: полигидроксибутирату (ПГБ) микробиологического происхождения, полилактиду и другим полимерам на основе полимолочной кислоты, поликапролактону. Рассмотрены их модификации с такими добавками, как гидроксиапатит, хитин и хитозан и бета-трикальцийфосфат. По итогам работы наиболее перспективными оказались материалы на основе ПГБ благодаря его полной биоразлагаемости на нетоксичные для организма продукты (углекислый газ и вода) и хорошей биосовместимости. Тем не менее, существующие композиции на основе ПГБ имеют недостатки, к которым относятся хрупкость, низкая эластичность, нестабильное поведение при высокотемпературном воздействии при переработке, формовании имплантатов, стерилизации и др. Это требует доработки композиций как в плане модификации полимера, так и по составу.*

Выводы. *В обзоре рассмотрены подходы к достижению свойств материалов, требуемых для совершенных имплантатов. Основными требованиями, предъявляемыми к имплантатам, являются оптимизация времени резорбции остеопластического матрикса, облегчение рассасывания остеопластического матрикса, синхронизированного по времени с процессом регенерации кости. Для достижения этих требований необходимо применять технологии, которые включают модификацию ПКМ путем воздействия на химический состав и структуру; введение наполнителей; использование химической функционализации, ориентационной вытяжки, термической обработки. Успех использования костных материалов на основе биодеградируемых полимеров основан на точном понимании механизма действия различных компонентов композиции для имплантата и строгом соответствии с ужесточающимися нормативными требованиями технологии имплантации.*

Ключевые слова: *остеопластические материалы, регенеративная медицина, тканевая инженерия, остеогенез, материал для костных имплантатов, биодеградируемые матриксы, полиалканоаты, гидроксиаппатит, биоактивность костных имплантатов, молекулярная структура материала для имплантатов*

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INTRODUCTION

Much research attention is currently being paid to areas of medicine involving the development and production of various osteoplastic (bone-substituting) materials [1–7]. These materials are in demand in dentistry, maxillofacial surgery, as well as various areas of bone surgery.

The requirements for the nature and quality of materials intended for the manufacture of implants, as well as technologies for their manufacture, are determined by the application and conditions of functioning of implants and endoprostheses in contact with living tissues.

A common requirement related to the properties of materials for implants is the presence of osteoplastic and osteoconductive properties that support the formation of conductors for the germination of blood vessels with subsequent resorption and replacement with bone tissue. Osteoconductive materials serve as a matrix for the formation of new bone during reparative osteogenesis and have the ability to direct the growth of bone tissue. Implants require hydrophilic properties. Surgical interventions in bone surgery are often associated with pre-infected pathological foci where surgical treatment often is performed due to the development of inflammatory complications. An important problem is the choice of resistant (proof against infections) materials, as well as materials that do not cause thrombosis.

Despite impressive advances achieved in the development of a new generation of osteoplastic materials for bone implant purposes in recent decades, involving work carried out by world-leading research centers conducting experimental and clinical studies of osteoplastic matrices, as well as the devotion of significant material and financial resources to the field of regenerative medicine, a number of unresolved issues remain. These include optimizing the time of resorption of the osteoplastic matrix and the best choice of an effective technology to facilitate the resorption of the osteoplastic matrix synchronized in time with the process of bone regeneration. As a result, the review by D.D. Lykoshin and co-authors [8] shows that autografts still remain the gold standard in clinical practice.

Scientists are searching for materials and compositions having osteoplastic properties, which are at the same time resistant to bacterial influences. Recently, the range of materials with the above properties has been greatly expanded due to the use of synthetic materials, including biopolymers and various other biodegradable compositions. Biopolymer materials are often completely non-immunogenic, can be sterilized by modern medical methods, and are relatively inexpensive to produce. However, the most valuable advantage consists in their wide range of physicomechanical and biochemical properties due to the possibility to regulate of the supramolecular and molecular structure of polymers.

The broadest requirements for materials for implants are realized when using biodegradable compositions. Biodegradable polymer composite materials (PCMs), which are designed to create bioresorbable (gradually dissolving in the body) implants, comprise complex engineering tools from which biologically compatible systems can be constructed. The creation of such a system should be accompanied by the establishment of factors affecting bioresorbability. Thus, there are problems of studying the effect of the initial morphology and structure of PCM used for bioresorbable implants on their properties and qualities. Another important issue is the influence of the technological parameters of the manufacture of PCM on the properties of the implants obtained from them. In order to predict the quality of the implants obtained, it is important to identify the role of the structure of the material in its biological activity relative to the biological environment and body tissues with which the implants made of this material are intended to interact.

When selecting a biodegradable material for bioresorbable implants, as well as in the manufacture of the prosthesis itself, numerous technological problems arise. For example, the use of biodegradable polymer materials is greatly limited by a lack of deformability (elasticity), which is necessary due to most of the bones of the human body being subjected to cyclic loads, gradually leading to an increase in the concentration of stresses in the microstructure of the product and eventually destroying it. It is also important to note that the body's immune response to biopolymer materials in contact with it occurs at various levels, from single molecular interactions to complex perception of volumetric biophysical properties that coordinate reactions at tissue- and system levels.

When creating a PCM implant, the material's osteoinductivity, i.e., the ability to stimulate osteogenesis when it is introduced into the body, leading to the activation of progenitor cells, as well as their proliferation and differentiation into osteogenic cells, becomes an important factor [9]. In this regard, when developing materials for implants, the problem arises of forming a structural organization of the PCM that contributes to the overgrowth of the implant with body cells. This can be achieved by creating a porous morphology (Fig. 1) [9]. At the same time, the formation of a certain porosity is required, i.e., the volume in the material occupied by pores along with the necessary structural characteristics (isolated or combined pores), as well as individual shape and size.

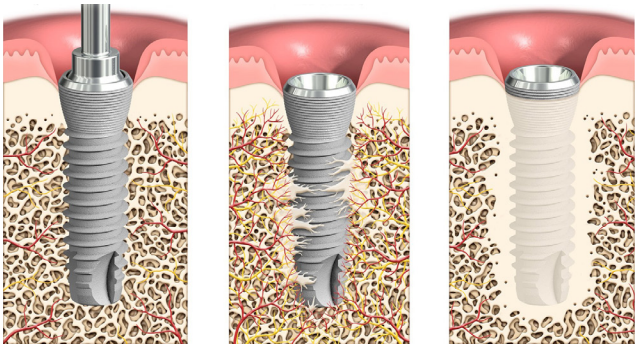

Fig. 1. Overgrowth of bone implants with cells of a living organism – osteogenesis [9].

Another method for achieving osseogenesis involves the use of mineral or organic fillers, drugs with the ability to initiate cell growth and development [10–14]; in any case, the presence of pores enhances this ability due to the sorption of drugs on the inner surface of the pores.

OBJECTIVES OF THE USE OF BIODEGRADABLE MATERIALS IN BONE SURGERY

Biopolymer composites are widely used in dental implantation surgery and dentistry. At the same time, the implantation of biodegradable polymer compositions for the treatment of bone injuries, defects, and fractures is still significantly limited due to the difficulty of achieving the required level of bioresorbability and osteoinductivity of implants made from these materials, as well as due to insufficient research base on the behavior of implants placed in a living organism and arriving there for a long time (Fig. 2) [15].

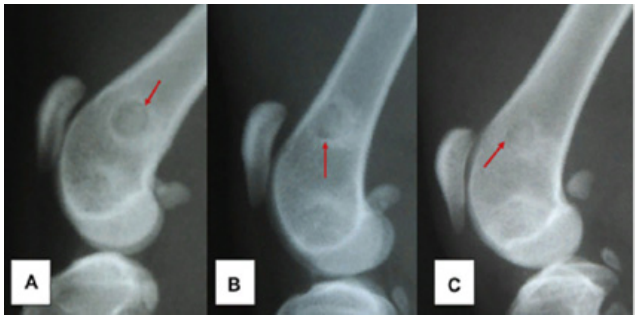

Fig. 2. Radiography of the distal femoral region of cats, where 70% of polyhydroxybutirate (PHB) and 30% of hydroxyapatite (HA) composite were implanted. The arrow indicates the decrease in the radiotransparent line around the implant over time. (A) Evaluation time in 30 days; (B) evaluation time in 60 days; (C) evaluation time in 90 days [15].

The mechanism of interaction between the implant and the body is based on the processes occurring at the bone–implant interface. The nature of the interaction between living bone cells and macromolecules of the polymer implant material at this boundary is determined by properties such as biocompatibility, corrosion resistance and cytotoxicity (Fig. 3) [15].

As established in [16, 17], such interaction depends on the surface topography, volume composition and morphology of the implant. The implant surface should be able to induce direct contact and functional connection between the implant and the bone tissue on which the load (osseointegration) is applied regardless of the area of location and the bone density, as well as its

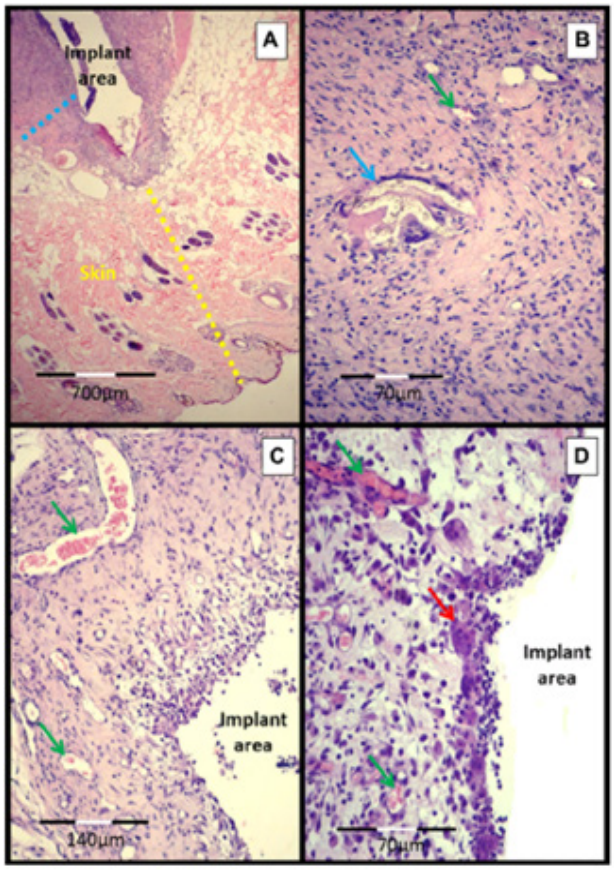

Fig. 3. Orthopedic implant made of a composite containing PHB and HA. Microphotography of the interface of a subcutaneous implant 45 days after an experimental operation to implant a composite of 70% PHB + 30% HA into the subcutaneous tissue of cats. (A) Skin (yellow dotted line), subcutaneous tissue and fibrous capsule or implant (blue dotted line). (B) Fibrous capsule in greater detail, showing the biomaterial (birefringent appearance) towards the giant cell (blue arrow), the green arrow points to the vessel. (C) Fibrous capsule with intensive neovascularization (green arrows) and (D) multinucleated giant cells (red arrow) [15].

quantity [18]. After the implant is installed, the contact area immediately provides the necessary stability due to friction and mechanical blocking forces between the bone trabeculae and the surface of the implant thread, leading to the development of new bone structure that replaces that surrounding the implant [2].

It is important to note that, while contemporary metal composites provide implants with the necessary strength and wear resistance, they have a big disadvantage due to the difference in the gradients of elastic modulus at the border with the bone, leading to tissue injury during the transfer of the occlusal load by the implant [3]. For ceramic products based on ZrO_2 and TiO_2, studies of such problems caused by the high modulus of elasticity of zirconium dioxide, showed how this can lead to the destruction of bone tissue [4]. As well as overcoming this disadvantage, polymer materials offer a number of additional advantages associated with the bioresorbability and osseointegration of the material.

In the process of osseointegration of a bone replacement product, the interaction between the implant material and bone tissue should support the formation of fibrous tissue around the surface of the PCM leading to its improved structural stability [5]. Achieving such a state in full is often impossible due to the presence of a large number of variable factors affecting this process, among which are included the surface characteristics of the implant, the state of damaged bone tissue, the presence of bacterial infection, and the nature of mechanical loads exerted on the bone–implant system [2].

For a more complete understanding of the requirements for biopolymer materials and the necessary characteristics of these materials, it is necessary to establish the patterns according to which the biodegradation and integration of the material in the body takes place, as well as to understand the features of the osteogenesis process under the conditions of a foreign body introduced into the injured area of the body and its gradual destruction under the action of a biological media (Fig. 3) [8].

PATTERNS OF BIODEGRADATION AND BIOREPARATION OF A BONE IMPLANT

Bone is one of the few tissues whose fracture can heal without the formation of a fibrous scar. A fracture occurs due to exceeding the limits of tensile strength and deformation. The new formation of bone material in the process of fracture healing depends on the size of the gap at the fracture site [19]. The use of polymer materials for implants depends on the individual characteristics of the body, the type of injury and the mechanism of implantation. At the same time, it is necessary to distinguish between two types of osteogenesis: contact and distant. During contact osteogenesis, bone tissue is formed directly on the surface of the implanted product [13]. With distant osteogenesis, bone tissue regeneration occurs around the implant, i.e., new bone tissue spreads from the surface of the unaffected bone area to the implant [13]. Also involved in these processes are multipotent mesenchymal stromal cells (MMSCs), which are able to differentiate into bone (osteoblasts) or cartilage (chondrocytes) tissue.

Thus, the role of a polymer scaffold is to act a carrier of various growth factors (morphogenetic proteins that stimulate bone mineralization, fibroblast growth factors that enhance osteoblast proliferation, growth peptides that stimulate vascularization of the internal volume of the implant, etc.) at the same time as not triggering rejection by the body [20]. The fundamental characteristic of the implant is the dynamics of its biodegradation and the mechanism of the process. From the time of implantation to the completion of the bone remodeling phase, the strength interaction of the implant and bone at all stages of healing should correspond to one basic principle—the total strength of the bone–implant system at any time should not be lower than the final target bone strength after healing [21]. However, regarding the stability of the bone–implant system, according to studies in dental implantology [13, 18, 22, 23], the total stability changes have a V-shaped profile and may fall to 55–65% of the target in the middle of the healing cycle due to a more intensive decrease in primary stability due to bone resorption in those places where the implant coils exert pressure on the bone trabeculae causing the death of osteocytes. Although secondary stability (the formation of new bone tissue on the surface of the implant) increases over time, its increase fails to compensate for decline in the primary stability in the interval from 15 to 40 days after implantation, resulting in a fall in overall stability.

Although the implant is expected not to completely collapse after three phases until the fracture is completely healed, at the same time, the implant must completely dissolve within 3–6 months after healing in order to exclude a negative reaction of the body to a foreign body. In the case of bone implants, it is important to refer to individual structures of a certain shape, size and strength, on which the features of the biodegradation process of the composition and the possibility of regulating the decomposition rate at the stage of obtaining a polymer material depend, for example, during subsequent 3D printing [21, 24].

Biodegradation of an implant in contact with living cells of the body is a complex multi-stage process involving a number of physical stages and chemical reactions:

– polymer dissolution;

– ionization of ionogenic groups present in polymer macromolecules;

– ionization of ionogenic groups formed during the reactions of destruction and hydrolysis of polymer macromolecules;

– destruction of polymer–polymer complexes;

– hydrolysis of polymer macromolecules;

– dissolution of the products of decomposition reactions in a polymer matrix [25].

The process of biodegradation of PCM in the body can be divided into two mechanisms: degradation of the material in the external diffusion-kinetic region (destruction of the polymer surface); propagation of degradation from the surface into the volume of the polymer matrix. It is important to note that several factors influence the surface and bulk degradation of the polymer. When the external area of the implant is destroyed, the chemical structure of the material, its morphology, the shape and size of the particles of the dispersed phase (filler), the nature of the pores and the degree of porosity of the material, as well as the presence of perforation of the implant play a key role [25, 26].

The penetrating ability of biodegradation is affected by the degree of swelling of the polymer in the biological media with which contact occurs (blood, lymph, synovial fluid). In addition, the relative rate of penetration of the biological medium into the material due to its swelling in comparison with the rate of decay of the surface layer plays a role. In this case, the diffusion parameters of the transfer of the biological medium play a role, due to the structure of the material and its chemical resistance. So, if the swelling rating is high, then the outer layer of the polymer does not have time to degrade, and the penetration of the biological medium into the volume leads to a gradual degradation of the inner layers. In this case, cracking may occur due to the rupture of strained bonds in macromolecules on the polymer surface and the subsequent mechanical destruction of the composite layers, which violates the integrity of the implant and reduces its mechanical characteristics [25, 27], as well as leading to an acceleration of the volumetric destruction of the implant as a whole.

In addition to rectifying unstable strength properties due to high swelling, control of the degree of swelling of the polymer composite plays an important role in the manufacture of bone implantation materials due to the problem of “clogging” the area to be repaired with mechanically destroyed, but not chemically decomposed fragments of the implant material. Thus, the higher the degree of crystallinity of crystallized polymers in volume, the lower their degree of swelling in water, and hence the lower the degree of penetration of enzymes that promote degradation into the polymer matrix [28].

In most cases, the destruction of the material in the surface layer occurs due to hydrolysis and enzymatic reactions [29]. This stage is non-cellular biodegradation, leading to the formation of microcracks in the material, deformation of the product and the formation of macro-cracks of various shapes and sizes.

The degree of destruction of PCM, which is determined by the composition, chemical nature and structure of the components, is most noticeable in areas with hydrophilic sites of macromolecules due to their more active hydrolysis. Over time, the outer layer becomes looser due to the formation of volumetric microchannels. For example, in [30], the creation of a polyhydroxybutyrate (PHB) composite with polyvinyl alcohol (PVA) having hydrophilic properties made it possible to regulate the moisture permeability of the material by changing the concentration of PVA. At the same time, although such a structure contributes to a more active penetration of the biological medium into the volume of the product, a favorable environment is already created for the splitting of water-soluble fragments of macromolecules outside the implant. Through a network of microchannels, the separated fragments can enter the biological environment, in which their further chemical cleavage into harmless molecules will occur under the action of mainly enzymatic hydrolysis.

It is worth noting that the hydrophilization of polymers, comprising one of the methods of their modification, can be carried out by plasma chemical treatment in an atmosphere of air or pure oxygen [31], in which the oxidation of the surface layer of the polymer material occurs due to the formation of polar groups containing oxygen (hydroxyl, carbonyl, carboxyl, etc.). This effect leads to an increase in the adhesive properties of materials.

In addition, hydrophilization can be carried out by treatment with other chemical processes: sulfonation, chlorosulfation, etching in organic solvents. When treated with a solvent, the surface layer of the polymer is loosened by its swelling, which leads to a weakening of the intermolecular bonds between the polymer chains in the near-surface layer [30].

After sufficient loosening of the outer layer of the implant, the process of cellular destruction begins under the action of monocytic phagocytes. After maturing into macrophages, these cells can concentrate on such a partially degraded surface, transform into epithelioid cell granulomas and coagulate into Langhans giant cells [10].

Langhans giant cells are giant multinucleated cells formed from epithelioid cells during their fusion or during the proliferation of macrophages. These cells can tighten sufficiently large macromolecules into their internal volume, envelop them with a cell membrane and process them at the expense of lysosomes and mitochondria. The beginning of the cellular destruction process and its dynamics are characterized by the size of the detached fragments of macromolecules, the degree of heterogeneity of the implant surface and the size of the protruding loosened fragments. Thus, it is believed that the sufficient size of such fragments for the active inclusion of phagocytic enzymatic hydrolysis is a fragment length of 20–30 μm. The photodestruction of biodegradable polymers (for example, during pretreatment of an implant) can increase the degree of crystallinity of the surface, which will lead to a decrease in the initial rate of enzymatic destruction and a decrease in the length of fragments necessary for its initiation [32]. In another study [33], it was shown that the rate of decomposition of PHB by enzymes is significantly affected by the molecular weight of the polymer and the temperature of destruction. For the human body temperature (37°C) at a molecular weight of 150 kDa in 3 months, the weight loss was 12%, and for high-molecular PHB (300–1000 kDa) only 2%. Consequently, varying the molecular weight of the polymer matrix can also significantly affect the rate of biodegradation.

The products of intracellular decomposition, depending on their composition, can be absorbed by these cells, or excreted into the circulatory system. Since the immune response weakens after some time (5–15 days) with sufficient polymer biocompatibility, the influx of macrophages at the site of the implant localization also decreases, allowing fibroblasts begin to form a tissue capsule. Loose connective tissue is embedded in the microcracks of the implant, followed by the stage of vascularization of the matrix and the germination of nerve-endings.

The germination of connective tissue depends on the morphology of the polymer, its chemical structure, and porosity, as well as the degree of destruction of the surface layer. The cellular stage usually begins quite a long time after the implant is inserted (closer to the reparative phase of fracture healing or the remodeling stage), which can vary greatly depending on the type of polymer [7, 10].

Thus, the sequence of stages of cellular destruction of the implant is reduced to the following:

– localization of macrophages on the implant;

– fusion of macrophages and their transformation into Langhans giant cells;

– activation of the mitochondria of Langhans giant cells in contact with the polymer matrix;

– enveloping of the separated polymer macromolecules and its further processing under the action of hydrolysis and fermentation;

– weakening of the immune response and the beginning of the germination of connective tissue.

Another problem manifesting itself at later stages of bone tissue healing is associated with the manifestation of various secondary processes, among which the most dangerous is excessive calcification of the surface layer of the implant. Since it will certainly come into contact with the bloodstream, the deposition of calcium salts (medium and basic calcium phosphates with different ion ratios) is an integral part of the implant integration process. Increased adsorption of calcium salts causes the formation of microcracks leading to the formation of a loose structure in the outer layer of the implant. The process of dystrophic calcification typically occurs as a response to soft tissue damage, which leads to the formation of significantly mineralized areas that cause blockage of blood vessels and can cause strokes and heart attacks. In this regard, reducing the degree of calcification represents an important problem. Studies demonstrating the effect of dexamethasone on transforming growth factor β1 responsible for cell proliferation and differentiation, as well as the ability of dexamethasone to act as an inhibitor of calcification, should be noted [34, 35]. Dystrophic calcification can also be reduced by modifying the polymer surface. This also contributes to the improvement of osseointegration and vascularization of the implant [10–12].

Since the formation of phosphates is an integral stage of degradation of the composite in the body, workarounds are needed to reduce the degree of their adsorption. This can be done by modifying the implant surface, for example, by introducing hydrophilic fillers into the PCM, forming layers on the polymer surface, or by changing the surface charge due to various drugs (heparin, protamine sulfate, etc.).

The authors of [36] developed and investigated experimental porous 3D carriers made of poly-3-hydroxybutyrate, designed for the restoration of bone tissue defects. The ability of the developed 3D carriers to support adhesion, proliferation and directed differentiation of cells in the osteoblastic direction was studied using the example of MMSC culture isolated from bone marrow and adipose tissue. Based on the results, the differentiation of MMSCs into osteoblasts was confirmed and measured. An increase in the expression of genes for osteocalcin, which is the most informative marker of bone formation, was revealed. Its release and entry into the blood occurs during osteosynthesis from osteoblasts.

REQUIREMENTS FOR DEGRADABLE PCMs FOR BIOMEDICAL APPLICATIONS

To create bone implants, it is necessary to develop a biodegradable material with the necessary deformation properties, strength, capable of with standing high-temperature exposure during 3D modeling of the implant [37], as well as ensuring its sterilization. At the same time, the achievement of an optimal biological reaction between the implant and the cells developing on its surface is realized if the implant has a micro- and macroporous structure [38].

A pore surface from 40 μm to 1 mm is the main factor ensuring cell germination [39, 40]. Under conditions of porosity, especially internal continuous porous areas in the polymer material, the cells of the body can easily attach to the inner surface of the pores and germinate through the entire implant, with the formation of blood vessels [41, 42].

In addition, the material should minimize the possible negative reaction of body tissues to foreign inclusion, not support or prevent the growth of bacteria on its surface, and avoid triggering an allergic or immune response of the host body. In terms of its mechanical characteristics, with the exception of various individual features of the damaged area of bone tissue and the localization of injury, the material should have high shear and tensile strength.

To provide parameters for the biodegradation process of an individually tunable bone repair material depending on the patient's age, presence or absence of infectious infection, tissue conditions near the affected area, and type and size of the lesion, fine-tuning of the decomposition conditions is necessary to vary the dynamics of material strength, mass, volume and size, taking into account the kinetics of bone tissue healing.

Thus, the role of the PCM structure for biomedical use in bone surgery should be considered from the perspective of three aspects:

– morphological aspect (structure of amorphous and crystalline regions): the size and shape of the polymer matrix crystallites, the amount of free volume in the composite for cell proliferation and differentiation into osteoblasts;

– pore formation (the ability of a material to form pores of a certain structure): porosity parameters include pore size and shape, the presence of isolated or combined pores and connections between them;

– reactivity (parameters of biodegradation of the material): chemical destruction, mechanical destruction of the composite due to overstressed bonds in macromolecules and the formation of microcracks, the formation of macrocracks due to the rupture of layers of the material by germinating cells.

By setting the optimal ratios between these aspects, it is possible to create a biodegradable polymer composite suitable for bone implantation. The condition for this adjustment is such a ratio between their contributions that the rate of implant biodegradation and the associated loss of strength does not exceed the rate of increase in the strength of newly formed bone material.

OVERVIEW OF POLYMER MATERIALS SUITABLE FOR USE IN IMPLANTATION

To date, various synthetic and natural polymer materials, as well as mineral-based materials, have been created and used for bone and dental implants. Among the mineral materials that have been widely used, it should be noted hydroxyapatite (HA), beta-tricalcium phosphate (β-TCP) and ceramics, including organic (collagen) and natural biopolymers (polysaccharides) variants.

Among the mineral components, HA is the most promising due to its excellent biocompatibility, as well as ability stimulate osteogenesis and form a matrix for the formation of new bone tissue. Nanocrystalline HA is able to more actively adsorb proteins necessary for the vital activity of cells [43], while according to [44] its ability to stimulate reparative osteogenesis is even higher than that of polycrystalline HA.

In [45], a method for the synthesis of nanoscale HA was developed along with a proposed method for its purification and methods for the formation of porous calcium-phosphate composites based on HA and collagen. The methods described in the article make it possible to produce tissue-engineered structures offering an adjustable architecture for solving various biomedical tasks.

Materials based on β-TCP are also thought to be quite promising [46] due to their high degree of degradation, excellent biocompatibility and the ability of this substance to create a matrix for the germination of osteoblasts in the process of reparative osteogenesis. However, due to the excessively rapid degradation of the material leading to a significant drop in its compressive strength, it cannot provide a basis for the formation of new bone tissue [47].

Calcium-phosphate ceramic materials are characterized by heterogeneity of the particle sizes of the material and pores [48], in connection with which work is underway to find more promising bone implantation materials.

Collagen is a filamentous protein that is the main component of connective tissue. Approximately 30–35% of all proteins in the human body and most mammals are made up of collagen, including most

of the joints, tendons, skin, walls of blood vessels, as well as forming part of nail-, tooth- and bone tissue. Collagen obtained from cattle tissues is generally appropriate and cost-effective.

Among polysaccharides, chitin-, chitosan-, alginate-, and starch-based materials have been widely used.

In modern medical science, technologies for the development of materials based on various polyolefins are considered, the possibilities for their use in replacement implantation surgery are studied. Despite the creation of polypropylene-based synthetic materials characterized by a high degree of biocompatibility [49], their use is associated with a number of disadvantages, such as the occurrence of postoperative complications due to rejection of the material by the body. For example, in [50], the inflammatory reaction of the body to the implantation of a polypropylene product was studied, during which it was found that 6 months after implantation, a tightly formed connective tissue formed around the material, while the leukocyte-lymphocyte inflammatory reaction to a foreign body remained throughout the entire period. At the same time, significantly fewer cells involved in phagocytosis were formed around the material than during the decomposition of biopolymer materials.

Compared with polyolefins, materials based on biopolymers obtained by chemical synthesis in living organisms—plants or microbial systems [6]—have a number of advantages. Such polymers have a more complex and well-defined structure compared to synthetic polymers and are characterized by high biodegradability and renewability.

One of the most promising biopolymers is a polymer based on lactic acid—polylactide (PLA). PLA is obtained from natural raw materials: rice, potatoes, corn, etc. Due to the bioabsorbability of PLA, it can be used as stents for implantation into the body without the need for repeated surgical intervention due to their complete biodegradation in a relatively short time [7, 8]. At the same time, the hemocompatibility of this polymer is comparable with the indicators of other materials used as stents such as stainless steel.

Composite frameworks based on PLA can be carriers for morphogenetic proteins that stimulate the formation of bone tissue [51].

In the study [52], PLA was compared with other biopolymers (polycaprolactone, chitosan, PHB). Histological data showed that, in addition to offering good supporting functions for connective and bone tissue, PLA does not cause pronounced inflammatory infiltration by lymphocytes, neutrophils and Langhans giant cells. The metabolites of the breakdown of PLA have no negative effect on the body or on the dynamics of osteogenesis as a whole. Based on the results of the work, the materials from the PLA are recognized as promising for use in veterinary bone surgery.

In addition to pure PLA, copolymers of PLA and polyglycolic acid (PLA–PGA) are more often used. Such copolymers are used as surgical decomposable screws, fingers, pins, and whole plates for the restoration and remodeling of bone defects, as well as the formation of cartilage tissue. Such copolymers are not cytotoxic, and the rate of their decomposition can be regulated by changing the ratio of components.

Another naturally degradable polymer of microbiological origin is poly-3-hydroxybutyrate (PHB, P-3-HB). Despite the presence of significant disadvantages of this material limiting its use in its pure form, which include thermal instability and high brittleness, a large number of studies are being conducted on the use of PHB in composite materials together with the introduction of a range of various fillers of both natural origin (including mineral) and synthetic [53–55] (including modifiers and plasticizers).

Studies on the regeneration of bone defects of various rat bones using PHB have shown that implantation of an element made of pure PHB or filled with mineral components of PHB does not worsen the conditions of bone tissue regeneration and does not cause an inflammatory reaction. In addition, the material usually has a high resorption capacity and promotes the propagation of the regeneration front towards the damaged area from the periphery to the center of the regenerate.

THE EFFECT OF PCM MODIFICATION ON THE STRUCTURE AND BIOLOGICAL ACTIVITY OF THE MATERIAL IN BIOLOGICAL MEDIA

The biodegradable capacity of polymers to be absorbed by microorganisms depends on a number of parameters and structural characteristics. The most important are the chemical nature of the polymer, the branching of the macromolecule (the presence and nature of side groups), as well as the molecular weight, supramolecular structure, structure of the crystalline regions, and the conformation of the chain in the amorphous region [7, 10]. Natural and synthetic polymers containing bonds that are easily hydrolyzed have a high biodegradability. The presence of substituents in a polymer chain often contributes to increased biodegradation. The latter also depends on the degree of chain substitution, the length

of its sections between functional groups, and the flexibility of macromolecules.

Thus, biodegradable polymers should:

1) be heterochain and contain bonds available for biodegradation: R=CH_2; R=CH–R_1; R–CH_2–OH; R–CH(OH)–R; R–CO–H; R–CO–R_1, etc.;

2) contain fragments that include no more than 5 groups of CH_2 in a row;

3) have volumetric substituents in the composition: the larger the volume of the substituent, the faster the polymer is destroyed;

4) include natural products in the macromolecular chain—starch, cellulose, lactose, urea, which can be used as fillers, and then microorganisms absorb them.

Polymers having an amorphous supramolecular structure are invariably less resistant to biodegradation than crystalline ones. This is due to the fact that the compact arrangement of structural fragments of semi-crystalline and crystalline polymers limits their swelling in water and prevents the penetration of enzymes into the polymer matrix, making it difficult for enzymes to act not only on the main carbon chain of the polymer, but also on the biodegradable parts of the chain.

An important factor determining the resistance of a polymer to biodegradation is the size of its molecules. While monomers or oligomers can be affected by microorganisms and serve as carbon sources for them, polymers with a large molecular weight are more resistant to the action of microorganisms.

Biodegradation of most technical polymers is usually initiated by non-biological processes (thermal, photo-oxidative, mechanical degradation, etc.). The mentioned degradation processes lead to a decrease in the molecular weight of the polymer. In this case, low-molecular bioassimilable fragments arise, having hydroxyl, carbonyl, or carboxyl groups at the ends of the chain. The resistance of polymer materials to the action of microorganisms also depends on the plasticizers, fillers, stabilizers, and other technological additives included in their composition, as well as on the extent to which these substances can be a source of carbon and nitrogen for microorganisms. It is known that inorganic components (silicates, sulfates, phosphates, carbonates) do not support the growth of fungi.

When creating biodegradable materials, the process of modifying synthetic polymers and composites using natural polymers has become widespread. An important place in the research is occupied by the problem of giving the properties of biodegradation to well-mastered multi-tonnage industrial polymers: polyethylene, polypropylene, polyvinyl chloride, polystyrene, polyethylene terephthalate, polyurethane. For this purpose, three modification directions are being actively developed [56]:

– admission of synthetic polymers of molecules containing functional groups, such as complex ether, amide, anhydride, urethane, etc. into the structure, with the presence of such groups promoting accelerated photodegradation of the polymer to provide the ability to sorption of water, hydrolysis, which results in the formation of water-soluble products;

– preparation of compositions of multi-tonnage polymers with biodegradable natural additives capable of initiating the decomposition of the main polymer to a certain extent;

– directed synthesis of biodegradable plastics based on industrially mastered synthetic products, in which it is possible to change the properties of the material by regulating the hydrophilic and hydrophobic properties of its surface.

The idea of creating a composition of various synthetic polymers with starch appeared in the 1970s. Thus, in the article [57] G.J. Griffin described the process of developing composites with starch based on low-density polyethylene to create biodegradable film materials for packaging. The addition of starch allowed the material to decompose without exposure to ultraviolet radiation and water. Soil microorganisms contribute to the swelling and hydrolysis of starch, the formation of dextrin and glucose molecules, an increase in the surface area of the composite material and further peroxide destruction of the polymer. The formed low molecular weight fragments are subsequently assimilated by soil microorganisms.

An important scientific direction in the creation of a new class of biodegradable materials is the creation of modifiers composed of hyperbranched polyether polyol-based surfactants. The works of V.I. Gomzyak *et al*. are devoted to the synthesis of such surfactants [58]. Surfactants based on super-branched biodegradable polyether polyols are widely used as modifiers of polymer materials. Their activity depends on the degree of branching [59]. Polyether polyols are also used as a basis for the production of biodegradable block copolyesters [60]. To date, such compounds are used in medicine for the manufacture of containers for the targeted delivery of medicinal substances, which opens up wide possibilities for regulating the issuance of medicinal contents in a living body.

The study of the role of modifying additives introduced into materials based on PHB, PLA, and other polymers had demonstrated their significant effect on the biological activity of PCM in biological media [61–65]. These additives also have a great impact on the biocompatibility, strength and proliferation of cells for the scaffold material: a temporary mechanical structure that mimics the extracellular matrix of bone tissue, serving to create an optimal

environment for the repair of damaged bone. In order for healing to occur at a high rate and without complications, the scaffold should not be rejected by mesenchymal stem cells. For successful completion of all stages of healing, a high level of adhesion between the implant and organic tissues is required; in some situations, this can be achieved by introducing stem cells at the site of the scaffold [61].

An effective scaffold should provide adequate physical support similar to real bone in order to stimulate bone regeneration while ensuring a continuous supply of nutrients and metabolites of tissues formed on the skeleton. The paper [63] demonstrates the effect of well-delaminated organo-modified montmorillonite clay on the PHB matrix. This increased modulus of elasticity of the system as a result of this modification can be traced by the results of transmission electron microscopy and X-ray diffraction analysis. To understand the influence of temperature on the mechanical properties of the frame, the modulus of elasticity was studied both at room temperature, at which the implant itself is installed in the body, and at 37°C, which corresponds to the physiological temperature of a human body. It was found that at room temperature, the modulus of elasticity increases by an amount from 40 to 90% at filler concentrations from 3 to 5%. At the temperature of the human body, the same characteristic was 25–50% higher than the initial indicators. This filler was also shown to significantly affects the surface roughness. The rougher topography of the implant promotes attachment and proliferation of osteoblast cells to the surface. Studies have shown that a significant degree of proliferation over a large surface area was observed already on the fourth day after cell culture. Osteoblasts were attached by branching microfilaments and the formation of lamellipodia and microarrays at the interface of the bone–implant phases. When studying the rate of proliferation of body tissue by cell division (proliferation) on human osteoblast cells when they were stained with a fluorescent dye, positive results were obtained after 7 days of incubation. The thermal stability of nanohybrid materials was improved by using a nanocomposite with a clay content of 5%. The structure of the PCM with a low clay content (up to 1–2%) was heterophase; here, while the stratified state prevailed, an increase in clay concentration to 3–5% was noted along with the increased prevalence of intercalated state with small individual fragments by which means stratification was detected. Thus, the inclusion of nanoclay and similar fillers based on montmorillonite can be used to increase the rigidity of the composite material and its thermal stability without affecting the biocompatibility of the material in comparison with that of pure PHB (Fig. 4).

Concerning the decomposability of PHB-based materials in the body and the body's response to the introduced foreign object, studies into suture materials and threads are relevant [64, 65]. Materials from PHB and from the copolymer of PHB with hydroxyvaleriate (PHB-co-3HV) following intramuscular implantation to experimental animals did not cause any acute diseases, vascular reaction at the implantation site or any side effects, such as purulent inflammation, necrosis, calcification of the fibrous capsule or the formation of a malignant tumor for a long period (up to 1 year) [64]. The tested monofilament sutures made of PHB and PHB-co-3HV demonstrated the necessary strength for the healing of muscle-fascial wounds [64].

In the article [65], the degradation of a monofilament filament made of PHB-co-3HV was investigated both in a lipase solution and during implantation into the tergal muscles of a rat. The results showed that the monofilament thread gradually lost its tensile strength, which was accompanied by a decrease in molecular weight. Implantation to a rat did not show noticeable body responses during degradation *in vivo*. Reactions to the foreign body were much weaker than those of chrome catgut, which is one of the most commonly used medical suture products.

It was found that the introduction of chitin/chitosan as a rigid filler into the PHB matrix improves mechanical properties [66]. However, the high cost and complexity of manufacturing such a composition is a limiting factor in their use. Since chitosan is susceptible to carbonation at high temperature in a mixture of melts, it is necessary to use a solution or other technology [66]. Compared with pure chitosan films, the mixture of PHB (30%)–chitosan (70%) showed higher tensile strength and elongation at break by 40% and 60%, respectively. In addition, these properties, combined with the porous structure of PHB–chitosan films, increase the likelihood of using these composites in tissue engineering.

When studying a mixture of PHB–chitin prepared by casting from a solution, the authors [67] established the formation of an intermolecular hydrogen bond between the carbonyl groups of PHB and the amino groups of chitin. At the same time, the crystallization process was accelerated due to heterogeneous nucleation on chitin particles, which contributed to the rapid growth of PHB crystals. However, decreased crystallinity at higher chitin concentrations can be explained by a concomitant decrease in the mobility of PHB chains due to intermolecular hydrogen bonds between PHB and chitin.

In the study [25], the structure and properties of biodegradable compositions based on PLA, chitosan and ethyl cellulose obtained in a Brabender

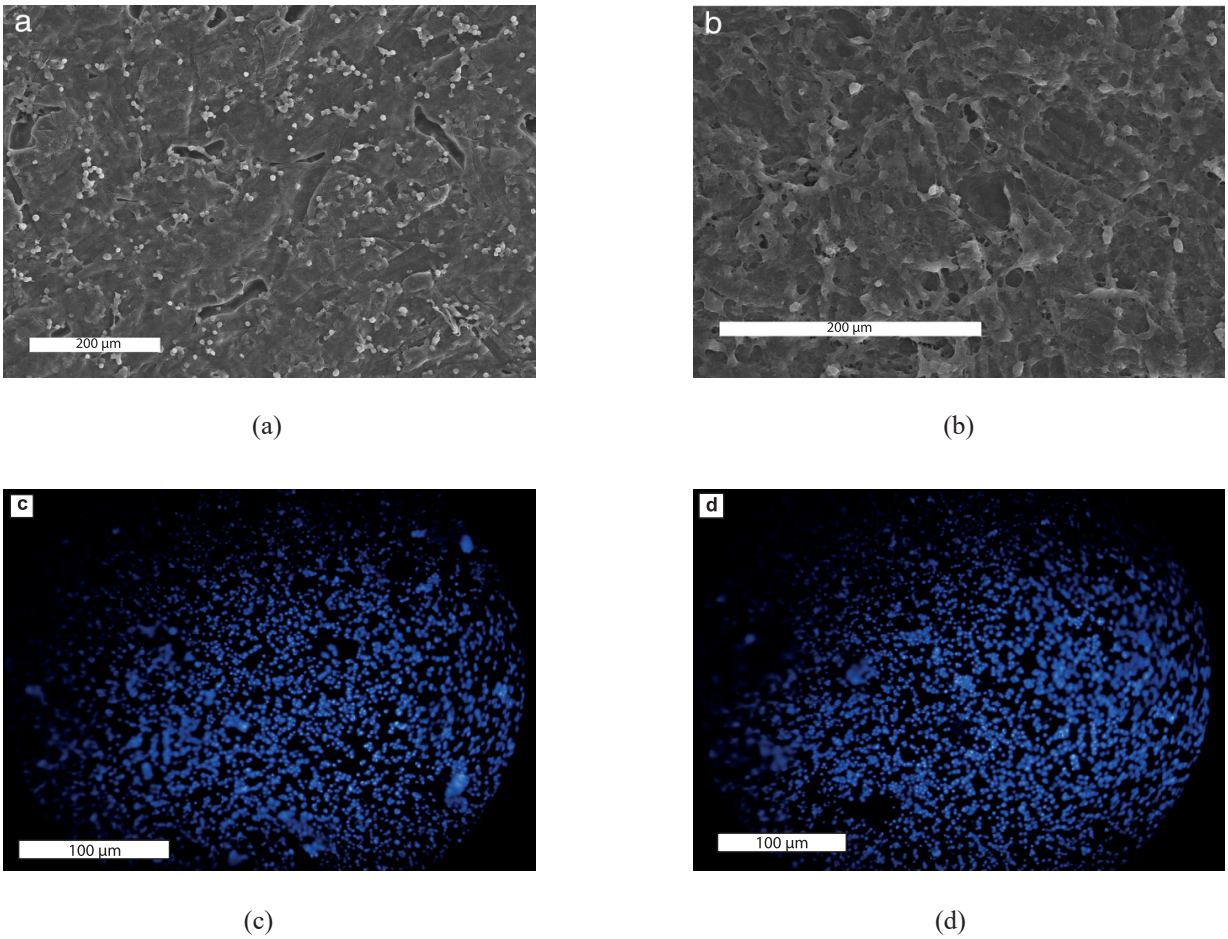

Fig. 4. SEM (300×) visualization of human osteoblast cells after 7 days of cultivation:
(a) on pure PHB; (b) on PHB/5, wt % clay.
Staining of 4′,6-diamidino-2-phenylindole cells of human osteoblasts after 7 days of cultivation:
(c) on pure PHB, (d) on PHB/5 wt % clay [63].

type mixer were studied. It was shown that the addition of low molecular weight polyethylene glycol leads to an increase in the elongation of rigid PLA–ethyl–cellulose compositions. At the same time, the compositions have a sufficient level of biodegradability as estimated by weight loss under conditions of exposure in the soil.

In [68], a polymer PHB–chitosan composition for prolonged transport of biologically active substances was developed and studied. It was shown that the ratio of components allows varying the sorption capacity of the drug carrier (rifampicin), as well as the profile of its release. During the decomposition of the biopolymer matrix, voluminal microcracks are formed, contributing to the gradual release of the drug enclosed inside into the biological environment. Such gradual release of the substance can be used in other ways, for example, by including growth factors in the composition that promote proliferation (vascular endothelial growth factor) and bone formation (morphogenetic proteins).

In [69], the thermal properties of a porous PLA were studied. Porophores based on ammonium carbonate in a solution of acetone and supercritical CO_2 were used to prepare the porous composition. It has been shown that pore formation leads to the destruction of the crystalline regions of the PLA, reducing the melting heat of the crystallites. Changes in the crystal structure of the matrix also occur under the action of polymer plasticization caused by exposure to high temperature with the influence of pore-forming gaseous reagents. The internal pressure of gases significantly disrupts the pore structure; by varying the kinetics of the formation of crystal structures when the polymer is cooled [69], it is possible to change the strength and elastic properties.

In the three-block copolymer PHB–PLA-poly-caprolactone, a decrease in the probability of formation of large crystallites was identified as due to a decrease in the length of oligomeric segments and a restriction of the mobility of the chain of PHB blocks [709]. These factors, which lead to an

increase in the flexibility of the material, have a positive effect on its biocompatibility.

EFFECT OF EXTRACTION AND HEAT TREATMENT ON THE MOLECULAR STRUCTURE OF POLYALKANOATES

Crystallization and the size of crystallites have a great influence on the mechanical and thermal properties of polymers. The exceptional stereochemical regularity and low density of nucleation in polyalkanoates, for example, in PHB, contributes to interspherolitic cracking. In addition, secondary crystallization of PHB during heat treatment occurs in such a way that amorphous intercrystalline regions are enriched with pass-through chains in an extremely straightened conformation, which reduces segmental mobility, leads to a change in the thickness of lamellae in the crystallite structure, causing embrittlement of the polymer, and, consequently, deteriorates the mechanical characteristics of PHB [71].

The improvement of the deformation properties of the material typically occurs along with a decrease in its strength [72–74]. However, since both of these parameters are important in the case of manufacturing bone replacement products, it is important to implement methods that increase flexibility without significantly reducing strength. In this regard, the combination of extraction, which changes the orientation of molecular chains along the direction of extraction, thermal annealing at elevated temperatures and re-aging at room temperature can eliminate secondary crystallization, improving the overall impact strength [23].

Mixing of PHB with chitosan changes the structure of the crystalline regions of PHB during heat treatment. High-temperature annealing of composites consists in alternating melting and crystallization cycles in a non-isothermal mode. It was shown in [68] that the interaction of the components leads to a more ordered structure of chitosan and a higher stability of PHB crystallites, since chitosan prevents the recrystallization of PHB during annealing. In addition, intermolecular hydrogen bonds formed in the composition were found to represent a factor affecting the structure of PHB crystallites; the scope of this effect, however, depends on the localization of bonds in the amorphous regions of the composite.

There are results of experimental studies on the production of films from ultrahigh molecular weight PHB (UMW PHB) by uniaxial broaching with annealing at 160°C, according to which the strength characteristics of such materials were significantly improved. Thus, in [75], this method allowed to increase the elongation at break by 10–60% and the tensile strength by 30% to 100 MPa. The results of other studies show that the addition of UMW PHB in small concentrations also gives a significant improvement in the mechanical characteristics of the resulting mixture due to the effect of nucleation. At the same time, the extraction and simultaneous annealing of the fiber makes it possible to combine two immiscible components, such as PHB–UMW PHB [76], or PHB–ethylene-methyl-acrylate-glycidyl-methacrylate copolymer [76].

The work of J.C.C. Yeo [53] reports key areas of research associated with increasing the strength of biodegradable polymers on the example of PHB (Fig. 5).

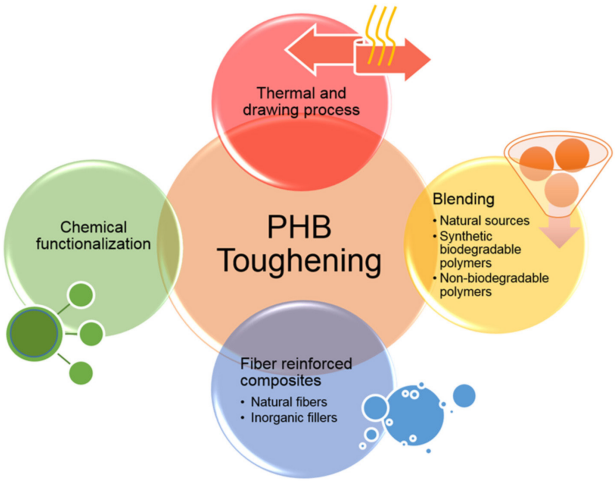

Fig. 5. Possible ways for hardening of PHB [53].

CONCLUSIONS

The development of a biodegradable composite material with excellent mechanical properties opens up new possibilities for the use of polymer materials in bone implantation surgery.

The present review has considered approaches to achieving this goal and identified requirements for a finished medical device, including optimization of the time of resorption of the osteoplastic matrix, facilitating its resorption, synchronization of the resorption time with the process of regeneration of bone material. Achieving these requirements is possible by introducing fillers, mixing with materials from natural sources, including synthetic biodegradable and non-biodegradable polymers, as well as the introduction of natural fibers or rigid fillers to form reinforced composites, modification by chemical functionalization, orientation extraction and heat treatment.

To date, due to their characteristics of biological compatibility and complete biodegradability into fragments that are non-toxic to the body, a number of polyalkanoates represent the most promising materials for further study. In future, the collective efforts of research groups working on materials of the polyalkanoate class are likely to significantly increase their popularity and distribution in the industry. It is to be anticipated that the success of using new bone materials based on biodegradable polymers will be due to a more accurate understanding of the mechanism of action of various components and strict compliance with regulatory requirements.

Authors' contributions

P.A. Povernov – literary review on the topic of the study, writing the text of the article;

L.S. Shibryaeva – the research idea, drawing up the outline of the study, assistance in writing the text;

L.R. Lyusova – consulting on the selection of materials for bone implants based on plastics and elastomers;

A.A. Popov – consulting on the creation of composite materials for medical purposes.

The authors declare no conflicts of interest.

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