Polymer and composite materials used in medicine – an overview

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Abstract: The article is a review of the literature on the use of polymers in medicine as biomaterials. Examples of the preparation of the most commonly used synthetic polymers in medicine, such as: polylactide (PLA), polyglycolide (PGA), polyhydrobutyrate (PHB), polycaprolactone (PCL) are described. The characteristics of ceramic materials: hydroxyapatite (HAp) and tricalcium phosphate (TCP) are also presented in terms of the use of synthetic biodegradable polymers as biofillers. The last part of article is devoted to the functional properties of composites based on PLA with the addition of HAp and TCP.

Keywords: polylactide (PLA), polyglycolide (PGA), polyhydrobutyrate (PHB), polycaprolactone (PCL), polymer composite materials, hydroxyapatite (HAp), tricalcium phosphate (TCP), applications of polymer-based materials in medicine

Materiały polimerowe i kompozytowe stosowane w medycynie – przegląd literaturowy

Streszczenie: Artykuł stanowi przegląd literatury dotyczący zastosowania polimerów w medycynie jako biomateriałów. Opisano przykłady otrzymywania najczęściej stosowanych syntetycznych polimerów w medycynie takich jak: polilaktyd (PLA), poliglikolid (PGA), polihydromaślan (PHB), polikaprolakton (PCL). Przedstawiono także charakterystykę materiałów ceramicznych: hydroksyapatytu (HAp) i trójfosforanu wapnia (TCP) pod kontem stosowania jako bionapełniacze syntetycznych biodegradowalnych polimerów. Ostatnia część artykułu jest poświęcona właściwościami użytkowym kompozytów na osnowie PLA z dodatkiem HAp i TCP.

Słowa kluczowe: polilaktyd (PLA), poliglikolid (PGA), polihydromaślan (PHB), polikaprolakton (PCL), polimerowe materiały kompozytowe, hydroksyapatyt (HAp), trójfosforan wapnia (TCP), zastosowania materiałów polimerowych w medycynie.

Characteristics of Polymers Used in Medicine

Polymers were first used in medicine as biomaterials in the 1950s to replace the cornea and blood vessels. The definition of the term “biomaterial” adopted by the European Society for Biomaterials reads “a biomaterial is a substance other than a drug or a combination of synthetic or natural substances that can be used at any time as part or whole of a system, replacing a tissue or organ, or performing its function”. Polymeric biomaterials offer a great variety as matrix and inclusion materials in the development of biocompatible, biostable, biodegradable or bioresorbable polymeric biocomposite materials for tissue engineering and regenerative medicine applications \cite{1}.

Due to the method of obtaining polymeric materials can be divided into natural polymers and synthetic polymers. Natural polymers provide certain properties, such as biocompatibility, biodegradability, low toxicity, while synthetic polymers provide other special characteristics, such as mechanical and physical properties, and chemical and thermal stability. On the other hand, synthetic polymers can be more easily processed into different shapes and different microstructures compared to natural polymers due to their sensitivity to processing conditions such as temperature, infrared or UV radiation.

Natural polymers are obtained from products of plant and animal origin. The most important groups of biomaterials are proteins, polysaccharides and polyesters. The most famous substances among polysaccharides are: hyaluronic acid, chitin and chitosan, cellulose, and...
among proteins - elastin and collagen. Natural polymers have proven useful in versatile applications including controlled drug delivery, gene delivery, regenerative medicine, and many others [2].

Synthetic polymers are very useful in the field of biomedicine because their properties (porosity, degradation time and mechanical properties) can be tailored to specific applications. They are often cheaper than natural polymers and can be produced in large quantities. The most commonly used synthetic polymers in medicine are polylactide – PLA, polyglycolide – PGA, polyhydrobutyrate – PHB and polycaprolactone – PCL [1].

**Polylactide – characteristics and properties**

Polylactic acid (PLA) is currently the most widely used biodegradable polymer in clinical applications. This is largely due to the favorable biocompatibility of the polymer and its safe degradation products. After coming into contact with the biological environment, the polymer begins to decompose, usually by hydrolysis, into lactic acid (LA) or into carbon dioxide and water [3]. The structural formula of racemic polylactide is shown below (Fig.1).

PLA is produced industrially by lactic acid polymerization or ring-opening polymerization of lactide. The first method uses direct polycondensation of lactic acid using organic solvents under high vacuum, where only low to medium molecular weight PLA can be produced. The method of obtaining PLA in the condensation reaction is presented below (Fig. 2).

In the second method, ring-opening polymerization of lactide is carried out without the use of a solvent. The second method is more commonly used because catalytic ring-opening polymerization of purified lactide yields high molecular weight PLA. In the first step of the lactide process, produced water is distilled off in a continuous condensation reaction, yielding low molecular weight oligomers or prepolymers. The prepolymer produced is then catalytically converted to cyclic lactide, and then purified by distillation under reduced pressure. In the next step, catalytic ring-opening polymerization of the purified lactide is carried out using a tin octoate catalyst or other organotin catalysts. After polymerization, the remaining lactide monomer is removed and recycled [4]. The figure shows the reaction for obtaining PLA by polymerization (Fig. 3).

Many types of PLA with different isomer ratios can be created, and the thermal, mechanical and biodegradation properties of PLA depend on the choice and arrangement of stereoisomers in the polymer chains. For example, when the D content is greater than 20%, a fully amorphous polymer can be obtained, while highly crystalline PLA can only be obtained when the L content is greater than 90% [4].

Polylactide is biodegradable and recyclable as it breaks down by hydrolysis of the main ester groups and sometimes by microbial attack. It can also be easily thermally processed. Unfortunately, it also has some disadvantages, such as low ductility and high brittleness. PLA is the most used raw material in 3D printing [4]. It is used in medicine, including in controlled drug delivery and release systems, in hydrogels, for the production of orthopedic screws, as well as in tissue engineering [5].

![Fig.1. Structural formula of racemic polylactide](image1)

![Fig.2. A method of obtaining PLA by condensation](image2)

![Fig.3. A method of obtaining PLA by lactide opening polymerization](image3)
Polyglycolide – characteristics and properties

Polyglycolide or poly(glicolid acid) (PGA) is the simplest aliphatic polyester. It is a highly crystalline polymer (45-55%) with a high melting point (220–225°C) and a glass transition temperature (TG) of around 35–40°C. PGA is insoluble in many solvents due to its high crystallinity, soluble only in highly fluorinated solvents such as hexafluoroisopropanol (HFIP) up to a molecular weight of 45,000 g/mol [6]. The structural formula of polyglycolide is shown below (Fig. 4).

Poly(glycolic acid) can be obtained by many methods, starting from different substrates, and the products obtained in this way have various physicochemical properties. One method is direct polycondensation polymerization of synthetic glycolic acid. The diagram of her reaction is shown in Fig. 5. Polycondensation of glycolic acid is the simplest process to obtain PGA, but not the most efficient, because it gives a low molecular weight product. Initially, the glycolic acid is heated at atmospheric pressure and at a temperature of about 175–185°C and held until the water ceases to distill. The pressure is then lowered to 150 mm Hg, still maintaining the temperature unchanged for about two hours. As a result, we obtain low molecular weight poly(glycolic acid) [7].

Another method of obtaining PGA is ring-opening polymerization of glycolide, a cyclic dimer of glycolic acid [8]. In order to obtain a glycolide, glycolic acid is heated under reduced pressure in the presence of a catalyst to form PGA oligomers. Further heating of these oligomers under reduced pressure produces a glycolide which is removed by distillation. The obtained glycolide requires further purification to remove traces of water and glycolic acid [7].

Polycaprolactone – characteristics and properties

Polycaprolactone (PCL) is an aliphatic polyester consisting of repeating hexanoate units. Its structural formula is shown in Fig. 7. It is a semi-crystalline polymer with a degree of crystallinity of up to 69%. PCL is soluble in many solvents at room temperature, such as dichloromethane, chloroform, tetrahydrofuran, benzene, carbon tetrachloride, toluene, cyclohexanone, etc. It has low solubility in acetone, dimethylformamide, ethyl acetate, acetonitrile. It is insoluble in ether and alcohol [9]. Excellent rheological and viscoelastic properties make PCL easy to manufacture. In addition, the mechanical properties of PCL make it suitable for medical applications that complement tissue engineering, such as wound dressing or dentistry, but also in other fields such as the environment, packaging and food [10].

There are two methods of PCL synthesis. The first one is the polycondensation of 6-hydroxyhexanoic acid (6-hydroxyhexanoic acid). The polycondensation is carried out under vacuum thereby removing the water produced during the reaction and shifting the equilibrium towards polymer formation. A method of PCL synthesis by polycondensation using Candida antarctica lipase and Pseudomonas lipase was developed [9]. This method has several disadvantages, such as prolonged reaction time, high reaction temperature, lack of exact stoichiometric equilibrium and the production of low-molecular polymers with high polydispersity values [11]. The ring-opening PCL reaction is shown in the figure below (Fig. 8). The second method is ring-opening polymerization (ROP). It yields a polymer with a higher molecular weight and lower polydispersity values, therefore it is a better way to obtain PCL than polycondensation. ROP synthesis can proceed through four main mechanisms that depend on the catalyst. There are anionic and cationic catalysts, ROP with activated monomer and coordination initiation [9].

Polycaprolactone proves to be a useful synthetic polyester due to its biodegradability, biocompatibility, mechanical properties, and slow degradation. It is easy...
to synthesize, and physical and mechanical properties can be changed by copolymerization [11].

**Polyhydroxybutyrate – characteristics and properties**

Polyhydroxybutyrate (PHB) is a linear polyester of D(-)-3-hydroxybutyrate and the best known of the related polyhydroxyalkanoate polymers, which is produced in microbial cells [12]. Its structural formula is shown in Fig. 9. PHB is highly crystalline due to its linear chain structure, containing both amorphous and crystalline phases [13]. It is a biodegradable plastic that can be degraded aerobically and anaerobically by soil microorganisms. It has similar physical properties as polypropylene, so it can be used as an alternative source of plastics [12].

The individual phases of PHB synthesis are catalyzed by specific enzymes. Their presence determines the correct course of individual reactions. The biosynthesis of poly-3-hydroxybutyric acid begins with the condensation of two acetyl-CoA molecules, catalyzed by the β-ketothiolase enzyme. The resulting acetoacetyl-CoA is reduced to 3-hydroxybutyrate-CoA under the influence of acetoacetil-CoA reductase. PHB synthase catalyzes the polymerization reaction of 3-hydroxybutyrate-CoA molecules (monomer units) to poly-3-hydroxybutyrate. During polymer elongation, PHB synthesis remains covalently bound to the molecular chain [14].

The main property of poly-3-hydroxybutyrate that distinguishes it from many other biodegradable polymers is its insolubility in water. The high resistance of the PHB biopolymer to hydrolytic degradation significantly extends its application. In addition, PHB is quite resistant to ultraviolet radiation. However, this polymer, in addition to many advantages, also has some disadvantages that limit its use or become a challenge for the industry. PHB is sensitive to acids and bases (especially concentrated ones) and dissolves in chloroform and other chlorinated hydrocarbons. The disadvantage of this biopolymer is also its brittleness at the level of 3–5%, which turns out to be particularly problematic when stretching the polymer [14].

**Fig. 7. PCL structural formula**

**POLYMER COMPOSITE MATERIALS USED IN MEDICINE**

Due to the rapid development of new biomedical technologies, including tissue engineering, regenerative medicine, gene therapy and controlled drug delivery, new materials are being developed to meet the specific requirements of these fields. Conventional one-component ceramic or polymer materials are not sufficient. In addition, in order to fully meet the basic requirements, such as biocompatibility, biodegradability, and appropriate mechanical properties, it is necessary to obtain materials that simultaneously fulfill several advanced functions. Therefore, key material and biological properties can be obtained through the design and development of multi-component materials, including the selection of matrix and filler materials, their parameters (e.g. shape, distribution, content), as well as composite manufacturing techniques. For this purpose, ceramic modifiers are introduced into biodegradable polymer matrices to obtain composites with specific properties for biomedical applications [15].

The composite material consists of two components, i.e. a matrix and a filler, also known as reinforcement or, more broadly, a dispersed phase. The matrix binds fragments of the filler, enables the products to be shaped appropriately and determines most of the physical and chemical properties of the material [16]. Polymer composites are widely used in many biomedical applications, such as applications in dentistry, tissue engineering and regenerative medicine [17].

The most commonly used materials that can be used as fillers in medicine are ceramic materials. Bioceramics can be of synthetic or natural origin, are designed to create connections with the bone and turned out to be an alternative to metal implants [18]. In the last few decades, calcium phosphate (CaP) ceramics have been widely used as a substitute for bone grafts, especially due to their chemical composition being similar to the mineral phase of bone. Due to its nature, calcium phosphate ceramics also show high biocompatibility and the ability to bond with bone tissue under certain conditions [15]. In addition to CaP, the most commonly used ceramics are alumina, zirconia and hydroxyapatite. Alumina and zirconium are bio-inert materials that exhibit high mechanical strength, excellent corrosion resistance, good wear resistance and good biocompatibility. Hydroxyapatite, on the other hand, is a bioactive material with excellent biocompatible properties [19]. Currently, ceramic materials HAp and TCP are quite commonly used materials for various biomedical applications [15].

**Hydroxyapatite (HAP) – characteristics and properties**

Hydroxyapatite with the chemical formula $\text{Ca}_{10} (\text{PO}_4)_6 (\text{OH})_2$ is an inorganic compound and is widely used as a bone substitute. It has chemical properties similar to hard tissues such as bones and teeth. It can also be used in the form of a fine powder as a filler, e.g. in tablets and capsules. Hydroxyapatite ceramic is bioactive, which means that when implanted into the human body, it promotes hard tissue ingrowth and osseointegration. The porous structure of this material can be adapted to the interfaces of the implant. The porosity of the hydroxyapatite structure can be controlled similarly to human bone, therefore it is ideal for use in implants for artifi-
cial teeth, hips and knees [20]. Stoichiometric HAp (Ca/P molar ratio 1.67) is believed to be osteoconductive but not osteoinductive. The solubility, bioactivity and biological response of HAp can be modified by anionic and cationic substitution. For these reasons, HAp is widely used in the production of polymer-ceramic composites, usually to impart bioactivity and osteoconductivity, as well as to improve mechanical properties [15]. HAp can be used as a filler for the following reasons: i) increases the biocompatibility of the substrate biomaterials (or matrix biomaterials) due to the similarity in structure and composition to natural bones and teeth, ii) inclusion of HAp particles in the polymer matrix may improve the degradation rate of composites, which is related to the percentage share of HA particles and an increase in their bioactivity, iii) HAp is considered a good bone graft material for creating strong chemical bonds between the implant and host bone tissues [21].

The most popular method of HAp synthesis is the precipitation method. It is also called wet precipitation, chemical precipitation or aqueous precipitation. This method is commonly chosen for HAp synthesis unlike other methods. The reactants are calcium hydroxide Ca(OH)₂ and orthophosphoric acid H₃PO₄. The only by-product of this re-action is water. The size, shape and surface area of the HAp particles obtained in this reaction are very sensitive to the rates of addition of orthophosphoric acid and the reaction temperature. The rate of addition of orthophosphoric acid is strongly related to the pH at the end of the synthesis, as well as to the stabilization of the suspension. The reaction temperature determines whether synthetic HAp crystals are monocrystalline or polycrystalline. HAp particles synthesized at low temperature (below 60°C) are monocrystalline [22, 23].

Tricalcium phosphate (TCP)

Tricalcium phosphate (TCP) has three polymorphs, which include α-TCP, β-TCP and α'-TCP. β-Tricalcium phosphate has been extensively studied and successfully used in clinical applications as a biomaterial for bone repair applications due to its remarkable biocompatibility, in vivo resorbability, bioactivity and good osteo conduc-
ductivity. In addition, some results indicate that TCP is considered osteoinductive. β-TCP has lower mechanical strength than HAp, however, β-TCP is more resorbable compared to HAp.

For many years, TCP has been combined with other ceramic materials such as HAp, Al₂O₃, ZrO₂ for the production of small dental or orthopedic implants in the form of composites or composite layers on implants. Recent decades have shown that the most promising form of TCP are small particles or nanoparticles that modify the biodegradable polymer matrix [15, 21].

β-TCP can be synthesized by solid state reaction, thermal conversion and precipitation. β-TCP can be produced by a solid-state reaction of a calcium-rich phase such as calcium carbonate (CaCO₃), calcium hydroxide (Ca(OH)₂), and HA with a phosphate-rich phase such as dicalcium phosphate (CaHPO₄), dicalcium phosphate dihydrate (CaHPO₄·2H₂O), calcium pyrophosphate (Ca₃P₂O₇), or ammonium phosphate ((NH₄)₃(HPO₄)). In order to obtain pure β-TCP, special attention should be paid to the thorough mixing of both raw materials. If the two components are distributed inhomogeneously impure phases may appear. For this purpose, an intermediate step of pre-sintering and homogenization (e.g. at 900°C) may be useful. Another common method of producing β-TCP is the thermal conversion of amorphous calcium phosphate. Typical raw materials used for aqueous precipitation are calcium nitrate (Ca(NO₃)₂), calcium hydroxide, ammonium phosphate ((NH₄)₃(HPO₄)) and phosphoric acid (H₃PO₄). When using calcium nitrate and ammonium phosphate, the reaction pH is kept constant by adding ammonia (NH₃) during the precipitation reaction. The β-TCP obtained as a result of conversion is more homogeneous than in the case of solid-state reaction [24, 25].

PLA/HAp composites

The introduction of hydroxyapatite to the PLA polymer matrix resulted in obtaining a PLA/HAp composite with high biocompatibility and high cell viability in vivo. The addition of apatite fillers also ensured the neutralization of byproducts formed during the decomposition of polylactide, which prevents the formation of inflammation in the body [26]. The PLA/HAp composite, due to its outstanding properties, has become a potential material for medical applications, mainly in areas such as tissue and regenerative engineering. In 2021, a group of scientists from Japan conducted research on the use of PLA/HAp composite as a carrier in drug delivery systems. In their research, they prepared a shell in the form of the considered composite by using the emulsion.
method. As a model drug, they used vitamin K1 due to its ability to dissolve in fats. The prepared samples were tested for drug loading and drug release in phosphate buffer solutions. Drug-loading studies have shown that as the amount of drug injected increases, the particle size also increases, proving that the shell is working properly. During tests of the release of vitamin K1 in a buffer solution, it was proved that the amount of the released vitamin increased with a decrease in the pH of the buffer, due to the fact that the HAp coating easily dissolved under acidic conditions. PLA/HAp particles have been found to be promising candidates as drug delivery vehicles due to their excellent drug loading capacity and pH sensitivity [27].

Due to the favorable properties of biodegradable polymers for medical applications, their copolymers are advantageous variants that make it possible to exclude their un-favorable disadvantages. Over the years, a wide variety of copolymers have been explored for bone repair applications, with poly(lactide-co-glycolide) copolymer becoming a promising material. In the paper, Hassan and other researchers developed a new bioactive, porous scaffold based on the aforementioned copolymer. They developed a composite based on poly(lactide-co-glycolide) (PLGA) with the addition of nano-hydroxyapatite with an admixture of strontium and zinc (Sr/Zn n-HAp). The obtained test results of this innovative composite showed that the developed material showed high porosity, and its bioactivity was proven by immersing the samples in a simulated body fluid. In addition, it was shown that the composite immersed in body fluid for a week had Sr, Ca, Zn ions in its structure, which in the case of implantation would increase the degree of osseointegration. The material also had good strength and biodegradable properties. One of the developed composites containing 2.5% Sr/Zn ad-mixture exhibited a compression behavior similar to that of bone tissue. The authors of the article announced further research into the use of this material for the production of bone implants [28].

In recent years, numerous studies have been conducted on modifications of PLA/HAp composites in order to accelerate the degradation of the composite scaffold. In their research, researchers from China developed a composite that additionally contained poly(glycolic acid) (PGA), due to its rapid degradation rate. Composite scaffolding was made using 3D laser printing. The obtained results showed that the inclusion of PGA increased the rate of degradation, as demonstrated by the increasing weight loss of the samples after one month of immersion in the PBS solution. This was due to the rapid degradation of the highly hydrophilic PGA and the subsequent accelerated hydrolysis of the PLLA chains. In addition, more pores were formed during degradation, which had a positive effect on the cell culture rate. The developed PLLA/PGA/HAp composite turned out to be a material with the desired biodegradable and biocompatible properties with human tissue, which makes this material a great potential for implantology applications, especially for the production of highly porous bone scaffolds [29].

PCL/HAP composites

Due to the fact that PCL has good processing and biodegradable properties, it is a very widely considered material for bone tissue regeneration, drug delivery systems and wound healing. In order to improve the connectivity between the tissue and implants made of PCL, hydroxyapatite was introduced into the polymer matrix. The introduction of an additive in the form of bioceramics made it possible to improve the mechanical properties and compatibility of the obtained products. In one of the articles from 2021, Montloung and other researchers examined how the reduction of the HAp content in the composite affects the properties of PCL and its further use in industry. The composite was prepared by using the melt-mixing technique, as this method is widely used in the industry. In the studies carried out, the amount of hydroxyapatite used varied from 1 to 7 wt%, which is a very small amount considering that in studies relating to medical applications, the amount of hydroxyapatite is up to 60%. It was shown that hydroxyapatite disperses much better at low concentrations in PCL, while agglomerations could be seen at higher contents of this additive. The mechanical properties of the obtained products, compared to the reference sample, improved with the increase in the hydroxyapatite content, although the researchers assumed their decrease due to the possibility of agglomeration in the composite. In addition, a significant decrease in crystallinity was observed with increasing bioceramic content, which could affect the strength properties. The conducted research showed that the developed composites can be used for various applications, including the production of foams and foils for packaging applications [30].

In 2021, researchers from Poland developed a three-component composite that can be used to produce bone scaffolds. The composite was developed on the basis of poly(ε-caprolactone), hydroxyapatite whiskers and L-lysine (Lys) were used as a filler. The scaffolds were made using the thermal alloy induction technique (TIPS). This technique makes it possible to modify the pore morphology in a simple way by deter-mining the appropriate thermodynamic parameters of the process. The resulting composite had a porosity of more than 90% and a much higher Young’s modulus than the PLA/HAp reference sample. By introducing L-lysine, the compressive strength was significantly improved. Researchers have shown that the resulting composite allows cell growth. In addition, the composite showed better biocompatibility compared to other PCL-based scaffolds, which means that the obtained three-component composite can be considered a good candidate for the production of biomedical devices [31].
CONCLUSIONS

Biomaterials are a promising class of materials with a wide range of applications in medicine to produce biomedical devices, such as hydrogel contact lenses, polymer or metal stents, artificial heart valves, steel joint and hip prostheses, knee and ligament implants, ceramic dental implants, polymer sutures, adhesives surgical. Properties such as biocompatibility, biodegradability and non-toxicity make these materials ideal for use in the manufacture of implants. The main purpose of implants is to mimic a body part and they are used to replace a damaged organ or structure to ensure the normal functioning of the body. Some of the most commonly used medical implants consist of heart, bone, eye, ear, knee, hip, and cardiovascular implants. Thanks to modern technologies and polymer materials, it is possible to produce implants with very precise shapes (3D printing), which allows them to be better adapted to the patient anatomical conditions. The polymers from which the implants are made are also characterized by high biocompatibility, which minimizes the risk of allergic reactions and rejection of the implant by the body. The polymer most used in 3D printing for medical applications is poly(lactic acid) (PLA).

With the development of 3D printing technology, one can expect an increasingly wider use of polymer implants in medicine, which will be more and more advanced and effective in the treatment of various diseases, including neurosurgical, orthopedic, and dental. The development of new technologies results in the development of new materials. Therefore, more and more research are being conducted on new materials and technologies that can be used in medicine.

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